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Effects of Breathing Air Containing Contaminants Such as CO2, CO and Hydrocarbons at 1 and 5 Atmospheres

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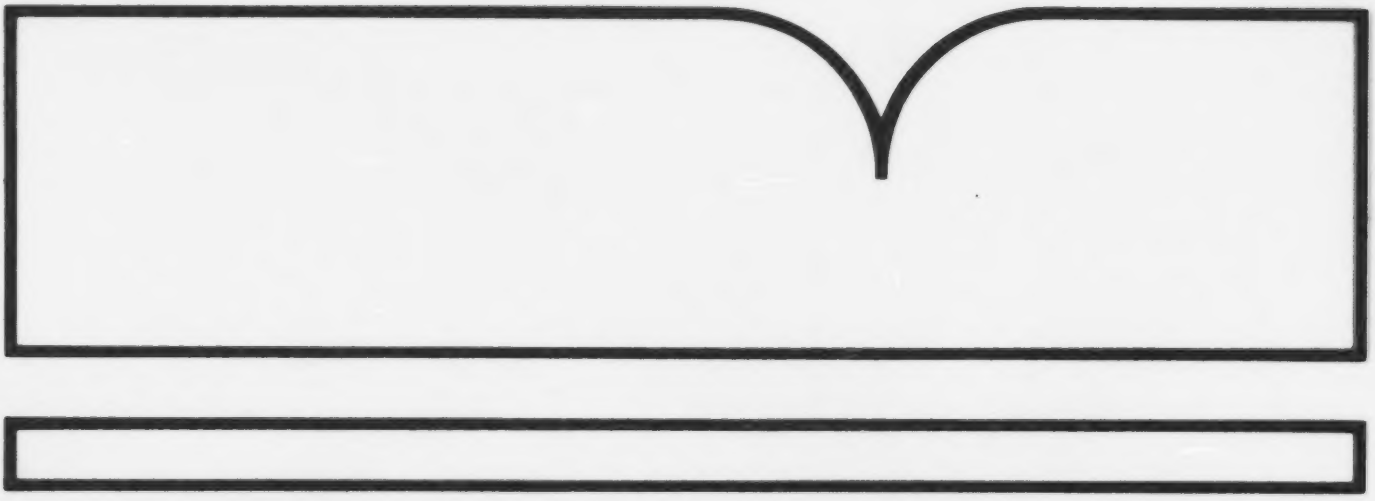

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EFFECTS OF BREATHING AIR CONTAINING CONTAMINANTS SUCH AS CO_2, CO AND HYDROCARBONS AT 1 AND 5 ATMOSPHERES

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16. ABSTRACT

The neural and behavioral effects of air contaminants such as CO_2, CO and hydrocarbons are reviewed. Each contaminant or contaminant class is reviewed separately and then an attempt is made to estimate effects of combinations of contaimminants. The effects are reviewed for both normobaric and hyperbaric conditions. Rough dose-effects curves were constructed from data found in the literature.

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EFFECTS OF CARBON DIOXIDE ON CENTRAL NERVOUS SYSTEM FUNCTION

Vernon A. Benignus

CO_2 NORMOBARIC

CEREBRAL EFFECTS

Blood Flow and Metabolic Rate. The administration of CO_2 in inspired air produces increased cerebral blood flow (CBF) via cerebral vasodilation, resulting in a correspondingly elevated cerebral tissue PO_2 which is a linear function of inhaled CO_2 (Szelenyi, 1970). The increased CBF appears to be homogeneous over grossly defined areas of the CNS (Maximilan et al., 1980; Sato et al, 1984). Similar results were found for cochlear blood flow (Hultcrantz et al, 1980) but retinal vessels were unresponsive to up to 5% CO_2 in inhaled air (Deutsch et al., 1983). Increased CBF to inspired CO_2 appears to occur independently of basal level of cerebral tissue PO_2 (Lavy and Carmon, 1969). The rise time for CBF after sudden administration of CO_2 is about 23 minutes and appears to be independent of CO_2 level (Shapiro et al., 1965; 1966a). CBF values return to normal in about one minute after sudden return to normal inhaled air CO_2 (Shapiro et al., 1966a) but large variability was reported. Newer data (Wilson et al., 1985) agree except that return to normal was longer (about 5 minutes).

The mechanism mediating the increased CBF is not known. The effect still occurs in a cerveau isole preparation (Lavy and Carmon, 1969) and for various kinds of central anesthesia

(Dahlgren et al., 1981; Hoffman et al., 1982; Kassel et al., 1981; Kliefoth et al., 1979; Sato et al., 1984) and in hypothermia (Lundar et al., 1986; Prough et al., 1986). Increased CBF is more closely related to venous than to arterial blood flow (Shapiro et al., 1966b; Wilson et al., 1985) which implies that cerebral tissue PCO_2 (or something related to it) is responsible for the increased CBF.

When man is engaged in problem solving, the CBF is increased in some but not all cerebral areas (Maximilian et al., 1980). When 6% CO_2 was administered in the same study, the profiles of the CBF were the same for rest and for problem solving. Only the baseline levels of CBF were shifted up by CO_2 breathing.

The cerebral metabolic rate of O_2 ($CMRO_2$) is apparently not affected by CO_2 inhalation (Artru and Michenfelder, 1980; Barzilay et al., 1985; Dahlgren et al., 1981; Hoffman et al., 1982; Kassell et al., 1981; Shapiro et al., 1966a) sufficient to produce even extreme hypercapnia, despite an earlier report of decreased $CMRO_2$ (Kliefoth et al., 1979). Thus, even though available O_2 (Szelenyi, 1970) is increased by CO_2 inhalation via CBF increases, the cerebral utilization of O_2 remains constant and appropriate to demand (Dahlgren et al., 1981). This conclusion probably holds for all levels of cerebral tissue PO_2 from normoxia and well above.

Electrophysiology. Inhalation of 5% or less CO_2 produces electroencephalographic (EEG) signs which may be interpreted as arousal (Gibbs et al., 1940; Harter, 1967; Ivanov, 1962; Lansing and Crown, 1969; Lavy and Carmon, 1969; Lavy and Tiberin, 1964;

Mattsson et al., 1972). Levels greater than about 6%, however produce EEG signs which are similar to early anesthesia (Gellhorn and Hailman, 1944; Harter, 1967; Mattsson et al., 1972). Auditory evoked potentials were slightly increased in latency by 5% CO_2 (Deecke et al., 1973) but the brainstem auditory evoked response was unaffected even by 10% CO_2 (Sohmer et al., 1982). When EEG is slowed by hypoxia addition of CO_2 (3-5%), ameliorates the effect (Gellhorn and Hailman, 1944; Rebuck et al., 1976).

The excitability of single cells in the CNS follows a similar pattern to the EEG. Below 5% inhaled CO_2, the effect was excitatory but at 5% and above the effect becomes depressant (Krnjevic et al., 1965; Morris, 1969). There was no effect of 5% CO_2 on the electroretinogram (ERG) but at 10% CO_2 the ERG amplitude was depressed (Niemeyer et al., 1982).

Apparently the single cell effects, and perhaps the effects of CO_2 on the EEG are not mediated by the increased CBF. In isolated cortical slabs, CO_2 administration did not produce increased CBF but did affect electrical activity (Soderberg, 1964). That the CBF autoregulatory mechanism was still intact, however, was demonstrated by the fact that CBF still increased with increased electrical activity.

Summary. Inhalation of CO_2 produces increased CBF over a wide range of hypercapnia. No effect on $CMRO_2$ is observed. Electrical activity is altered in an excitatory direction by CO_2 up to 4-5% but beyond about 6% the effect becomes depressant. Apparently the mechanism responsible for increased CBF is not the same as that responsible for electrophysiological effects.

Electrophysiological effects produced by hypoxia are to some extent reversible by inspiration of 3-5% CO_2.

BEHAVIORAL AND SENSORY EFFECTS

General. A description of the interoceptive and physiological effects of CO_2 in normoxia or hyperoxia is given by Lambertsen (1980). Below 3% CO_2 in inspired air, no effects are noticed. At 4% and above, respiratory stimulation proportional to the CO_2 level occurs, accompanied by generalized arousal. Dyspnea begins to occur between 7 and 10%.

The well known ventilatory response to inspiration of CO_2 is notoriously variable across subjects but apparently quite stable for a given subject (Singh, 1984). The response can be partially overridden for long periods of time by voluntary behaviors such as speaking (Phillipson et al., 1978), by hypnotic suggestion (Sato et al., 1986) and possibly by training (Florio et al., 1979). The ventilatory response to CO_2 was reduced by hypothermia (Ruiz, 1975) and by sleep deprivation (Sato et al., 1986).

Task Performance. As would be expected from the discussion of the effects of CO_2 on the CNS, administration of up to 5% CO_2 tends to ameliorate the deleterious effects of hypoxia upon memory and cognitive function (Gellhorn, 1937). Similar results are found in rhesus monkeys (Karl et al., 1978). The beneficial action of CO_2 administration is probably mediated via the increased CBF during hypoxia.

With normoxia or hyperoxia the effects of CO_2 administration have no effect or become harmful. With various O_2 levels from 21-50% and CO_2 levels up to 5% there were no effects of CO_2 on

simple or choice reaction time, short term memory, reasoning tests or pursuit rotor performance either while human subjects were at rest or exercising at 80% of maximum aerobic capacity (Sheehy et al., 1982). Using only two human subjects breathing 50% CO_2 in air, there were no effects on a motion compensation task but a simulated aircraft landing task was possibly slightly affected (Wamsley et al., 1969). Serial choice reaction time was increased in highly practiced young men by administration of 4% CO_2 in room air (Vercruyssen, 1984). Sleep stages were disturbed in rats when CO_2 level exceeded 5% (Ioffe et al., 1984).

Sensory Effects. Visual intensity discrimination which had been decremented by hypoxia was restored by administration of 3% CO_2 (Gellhorn, 1936). Again, this is a demonstration of compensatory increases in CBF and possibly ventilatory responses. In normoxia, however, 4% or greater CO_2 inhalation reduces auditory sensitivity (Gellhorn and Spiesman, 1935) and pain sensitivity (Stokes et al., 1948).

CO_2 - HYPERBARIC

The effects of CO_2 are related to the partial pressure of CO_2 in inspired air (Lambertsen, 1980). Thus any effect observed at e.g. 5% CO_2 at one atm would be expected to occur at 2.5% CO_2 at two atm and at 1.25% CO_2 at four atm. The prediction is supported by a study at extreme conditions (122 atm) using seizure activity as the dependent variable (MacGinnis et al., 1967) when CO_2 had to be reduced to .016%. Similarly, at hypobaric pressures, the percentage of CO_2 in inspired air can be increased without ill effects (Lambertsen, 1980).

At hyperbaric pressures the effects of CO_2 must be considered in the context of hyperbaric air toxicity (see chapter 2). Hesser et al. (1971) tested subjects at 6 atm with CO_2 partial pressures of either 0, 15, 29 or 44 mm Hg (0, .33., .64 and 1%) in air. The control condition was 1.3 atm of O_2 with the same CO_2 conditions, thus holding PIO_2 constant. The partial pressures of CO_2 produced 0, 2, 4 and 6% CO_2 in the 1 atm condition. Hyperbaric air per se, produced a 30% increase in number of tracking errors and a 13% increase in reading times on the Stroop test. The addition of CO_2 as above further increased tracking errors in both control and 6 atm conditions. Average errors increased ordinally with CO_2 level by about 6, 7 and 21%. Stroop scores were found to have significant parallel increases at control and at 6 atm conditions averaging 6, 13 and 25% for the three CO_2 levels.

Hesser et al. (1978) studied arithmetic ability and screwplate performance in an experiment which was identical to the above except that 8 atm air was used with the same three CO_2 partial pressures. In the 8 atm condition therefore there was 0, 0.25, 0.5 and 0.72% CO_2. Arithmetic performance was degraded by about 20% by 8 atm of compressed air or by compressed air plus 15 mm Hg CO_2. Compressed air plus 29 mm Hg of CO_2 degraded arithmetic by 36% and when CO_2 was 44 mm Hg, the degradation was 57%. Oddly, screwplate performance was not affected by 8 atm compressed air, but, CO_2 had equal effects on both compressed air and control conditions. The screwplate performance was

decremented by 4%, 6% and 15% by the three CO_2 levels.

From the above two studies it may be concluded that (a) cognitive abilities are affected by hyperbaric air, in agreement with chapter 2 (b) motor abilities are affected by hyperbaric air but to a lesser extent or a lower probability, also in agreement with chapter 2 and (c) that CO_2 added to either normal or hyperbaric air adds a constant increment of error. The latter statement indicates that CO_2 does not interact with compressed air narcosis but merely produces an additive effect.

The data of Hesser et al. (1971, 1978) agree with predictions of CO_2 effects based upon gas laws as discussed above. The products of the ambient pressures and the CO_2 partial pressures were nearly constant in the 1, 6 and 8 atm conditions and the effects were, for practical purposes the same at each ambient pressure.

CONCLUSIONS

Data on behavioral and sensory effects of CO_2 inhalation are sparse. Were it not for the internal consistency of the results and the consistency with physiological CNS effects, making conclusions would be hazardous. Given the consistencies in the body of evidence the following conclusions do not seem far fetched.

Beneficial effects of CO_2 occur when hypoxia has produced behavioral or cognitive deficits. In normoxia or hyperoxia no effect of CO_2 inhalation has been reported for CO_2 levels at 3% or less. Deleterious effects on psychomotor, cognitive and sensory functions begin to occur at 4-5% CO_2, along with respiratory stimulation and general arousal. There are

apparently electrophysiological arousal effects at lower CO_2 levels but these are not noticeable behaviorally. The deleterious effects of CO_2 on behavior and sensory systems are probably due to the effect of CO_2 on the excitatory state of neural tissue while the beneficial effect of CO_2 (which occurs only during hypoxia) is apparently due to the increased CBF.

As was done in chapter 2, the behavioral decrements due to CO_2 were converted to percent of control condition. Figure 1 is a plot of CO_2 concentration in percent against decrement in percent of control for motor and for cognitive behavior, using the data of Hesser et al. (1971, 1978).

Insert Figure 1 About Here

These curves are based upon limited data and should be treated with appropriate caution.

With considerable risk of inferential error, the data of figure 1 can be used to predict the decrements in hyperbaric air with CO_2 contamination. The data of Hesser et al. (1971, 1978) and the gas law hypothesis of Lambertsen (1980) justify such a procedure. Figure 2 shows the predicted curves for percent decrements in motor effects as a function of atm of pressure, in

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Insert Figures 2 and 3 About Here

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an air environment for CO_2 at 0, 30 and 46 mm Hg. Predictions for cognitive effects in an air environment are shown in figure 3.

Special caution should be used in the application of figures 2-3 since they are extrapolations based upon theory and only a little data. If water environments worsen compressed air toxicity, it is also possible that such an environment would worsen the additive CO_2 toxicity. No data exists on this question.

CARBON MONOXIDE (NORMOBARIC)

CNS Physiological Effects

O_2 Supply. Carbon monoxide (CO) in inhaled air binds quickly to hemoglobin to form carboxyhemoglobin (COHb) after passing through the alveolar membrane, in much the same manner as inhaled O_2 forms oxyhemoglobin (O_2Hb). CO is, however, retained by hemoglobin in preference to O_2 by a ratio of approximately 235:1. If hemoglobin were to release CO as easily as O_2, it would be possible to build up substantial tissue partial pressures of CO (PtCO). High values of PtCO have been shown to be toxic to cytochrome P-450 (Goldbaum et al., 1975, 1976; Walum et al., 1985). However, since COHb forms very rapidly, there is little physically dissolved CO left in arterial blood and therefore little CO available for uptake by other tissue.

The mechanism by which CO exerts its toxic effects in mammals is commonly accepted to be by the reduced O_2 carrying capacity of the blood (Coburn, 1979). While the blood O_2 carrying capacity is reduced by reducing the percent of hemoglobin available for O_2 binding, the presence of COHb in the blood or the reduction on O_2 supply triggers a compensatory increase in cerebral blood flow (Haggendal et al., 1966; Paulson,

1973; Traystman et al., 1977; Dobler et al., 1977; Traystman, 1978). Studies in dogs (Haggendal et al., 1966) indicated that the compensatory CBF did not occur until COHb values reached 20% and then continued to increase with further COHb increases. In humans the CBF did not increase until COHb reached values between 8 and 20% but at a COHb of 20% the CBF had increased by 20% (Paulson, 1973). Traystman (1978) showed that CBF in dogs increased in a dose related manner beginning at a COHb value of 2% CBF increased more rapidly above about 22% COHB as it did below that value. Traystman attributes the difference between his data and the results of others and previous studies to technical problems in earlier work.

The adequacy of compensatory responses of CBF in response to elevated COHb can be judged by the PtO_2 levels or, as a surrogate, the venous partial pressure of O_2 (PVO_2). Paulson, (1973) reported that in humans jugular PVO_2 fell by about 1 mm Hg at 8% COHb and by 3.4 mm Hg when COHb was 20%. Zorn (1972) presented data indicating that in cat, rat and rabbit brain, PtO_2 fell as a linear function of COHb. Similar results were reported by Miller and Wood (1974). It may be calculated that if no vasodilation occurred, PVO_2 for 20% COHb would fall by about 8 mm Hg(Forster, 1970; Permutt and Farhi, 1969). Thus it appears that PtO_2 falls by about half of the expected value (Paulson, 1973). If these figures are representative and the experiments are replicable, apparently the compensatory increase in CBF is not adequate to prevent the fall of PtO_2 due to elevated COHb.

The amount of O_2 consumption was measured by Traystman et al. (1977) and Traystman (1978) as a function of COHb in

anesthetized dogs. O_2 consumption did not change significantly until COHb exceeded 30%. These findings could be used to argue that the compensatory mechanisms of increased CBF were adequate. It must be cautioned, however, that the lowest non zero level of COHb in the above studies was 11%. Lower level data would be useful.

The issue of the degree of CNS hypoxia which is produced by elevation of COHb is not settled. From measurements of PtO_2, it would seem that tissue hypoxia does occur. From measures of CNS O_2 consumption, it may be argued that CNS tissue hypoxia, even though it occurs, does not affect O_2 utilization. The latter conclusion must be tempered by the fact that the subjects were anesthetized and therefore not making elevated O_2 demands by CNS activity.

Electrophysiology. A number of sensory evoked response studies have been conducted in humans with elevated COHb. Usually no effects were seen even at levels of COHb of 22 and 37% (Dinman, 1969) or 20% (Hosko, 1970). Groll-Knapp et al. (1972) reported a reduced amplitude slow wave evoked potential at COHb values estimated to be about 10%. Putz et al., (1976) reported small evoked potential changes with 5% COHb.

EEG studies were reported by a few investigators. Hosko (1970) did not find EEG changes at 20% COHb or below. Benignus et al. (1983) measured slight increases in the 8-12 Hz EEG frequency band which were not statistically significant but remarkably consistent across various conditions.

Pharmacokinetics.

The formation of COHb has been mathematically described by Coburn, Forster and Kane (1965) who derived a single compartment differential equation model. The so-called Coburn-Forster-Kane equation (CFKE) was originally derived for the description of endogenous levels or for the description of the equilibrated state. The CFKE has not been extensively tested for accuracy of prediction, especially for the case of short term exposures.

Major environmental factors in the formation rate of COHb are (a) concentration of CO in inspired air, and (b) alveolar ventilation rate. Of course increased CO concentration increases COHb formation as does increased alveolar ventilation. By use of the CFKE, figures 4, 5 and 6 have been constructed to depict the formation of COHb for various CO levels and alveolar ventilation rates, as functions of time. It is noteworthy that COHb changes

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Insert Figures 4-6 About Here

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quite slowly in response to environmental CO changes. It should also be pointed out that the prediction is in terms of alveolar ventilation, not minute ventilation. Use of the figures as nomograms must make sure the proper units are used.

No empirical information is available on COHb formation at hyperbaric pressure. The Coburn-Forster-Kane equation (1965) was used to predict COHb formation and elimination at 1 and 5 atmospheres of pressure, using an exposure level of 25 parts per million (ppm) with alveolar ventilation rates of 5-20 liters per

minute (lpm). Figures 7 and 8 show the results for COHb

Insert Figures 7-10 About Here

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formation and figures 9 and 10 for COHb elimination. These figures must be interpreted with considerable caution for a number of reasons. Firstly, the curves are predictions from a model which has not been tested in this context. Secondly, it was assumed that the breathing of CO-contaminated air was begun after all tissue partial pressures had equilibrated to the 5-atmosphere condition. Thirdly, any physiological changes correlated with pressure were not considered. The provisional conclusions which can be drawn from figures 7-8, however, are that (1) increased atmospheric pressure increases COHb formation rate but not the asymptotic level, and (2) increased atmospheric pressure increases the elimination rate of COHb.

CNS Functional Effects.

The literature on the motor, cognitive and sensory effect of elevated COHb is large and internally inconsistent. Because of the prominent disparity in findings, this review will be more evaluative in an attempt to ascribe reasons for such disagreement among reports. A general critique is offered before specific articles are reviewed.

General Critique. Double-blind studies are possible in CO research since CO has no sensory stimulation effect. When neither the subject nor the experimenter is informed about the exposure condition until after the data have been collected (exposure selected by machine or by someone who has no contact

with the subject) then it is not possible to accidentally prejudice the results. Since important consequences accrue from CO research in terms of future monetary and health effects, and, more immediately, in terms of research programs, such unconscious prejudice is quite likely. Unfortunately few studies of CO effects were conducted in a double-blind fashion. The potential importance of this is demonstrated in a study on which both double- and single-blind studies were run (Von Post-Lingen, 1964). CO effects were seen only in the single-blind condition.

The most commonly encountered problem in the CO literature is the application of anticonservative statistical tests of significance (Muller et al., 1984). Use of anticonservative statistics results in an overestimation of the likelihood of effects of a substance by falsely declaring effects to be significant. When such methods are employed, the reliability of an effect can only be judged by the consistency with which it is reported across investigators. The question of how much consistency is sufficient is not an easy one, except in the unusual cases where an effect is unanimously reported as some level of exposure. This problem is further aggravated by the fact that nonsignificant findings are frequently not published at all.

A major problem in CO toxicology is the fact that most studies are done with exposure levels near what is taken to be the threshold for an effect. Very few studies employ a series of exposure levels above threshold. For this reason, effects are poorly described and difficult to demonstrate in a reliable

fashion. This problem is in part due to the hesistancy to expose humans to CO levels which are otherwise taken to be harmful, even though only temporarily. Experimenters also fear accidents due to marginal, undetected health problems in subjects. Unless, however, a reliable estimate of concentration-response functions for the various behaviors of interest are available, it is distinctly possible that the dangers are being overestimated because of poor estimates of thresholds. Additionally, unless the trends are well documented, it is not possible to decide how dangerous a deleterious effect may be. Clearly, even though an effect may be deleterious on a short-term basis, it is not reasonable to prevent exposure until the "cost" is well understood.

Vigilance Effects. Impaired vigilance may be among the CNS effects of low level CO exposures. As will be seen presently, however, the results are not very consistent. Since many of the following studies are related by replication attempts, they will be discussed in groups.

Horvath et al. (1971) required subjects to detect the occurrence of a brighter light flash in a series of light flashes. CO exposure of 111 ppm for 120 minutes produced a significantly reduced detection rate compared to air-exposed and 26 ppm CO-exposed sessions. Subjects were exposed for 60 minutes and then performed the task for an additional 60 minutes during continued exposure. For the 111 ppm CO exposure the mean COHb at the end of exposure was 6.6%.

Three attempts to replicate the Horvath et al. (1971) study failed to find statistically significant effects. Christensen et

al. (1977) used a slightly altered version of the Horvath task and added a number of physiological measurements and maneuvers which were performed during the test. While their CO-exposed subjects (113 ppm) also showed trends in vigilance decrements in the same direction as those of Horvath et al. (1971), their results were not statistically significant.

Winneke (1974) also used the Horvath task but with a modified rest schedule and added feedback about performance. By use of a complicated exposure scheme, the highest exposure group reached a mean COHb level of 11.3% by the end of their sessions. No trends in behavioral results were due to CO in any group.

Roche et al. (1981) used a vigilance task similar to that of Horvath et al. (1971). CO was administered in a large bolus followed by a reduced maintenance level. No significant effects were found on vigilance behavior and no trends toward effects were reported.

Groll-Knapp et al. (1972) presented sparsely documented results using auditory signal detection. Tone pairs were presented where the second tone was sometimes "weaker" than the first and represented the signal. Subjects were exposed to 0, 50, 100 or 150 ppm for 2.5 hours but COHb was not measured. Detection rate dropped, in a concentration related fashion, beginning at 50 ppm.

The significance tests used by Groll-Knapp et al. (1972) were very anticonservative. Perhaps the consequences of such statistical practices are best illustrated in this case. Without publishing further data, the authors have twice mentioned

failures to replicate (Groll-Knapp et al., 1979; Haider et al., 1976).

Fodor and Winneke (1972) used short bursts of white noise as stimuli and subjects were required to detect infrequent bursts which were slightly less intense than others. Subjects were exposed to 0 or 50 ppm CO for 80 minutes and then, during continued exposure, performed three blocks of 45 minutes vigilance tests. No COHb measurements were taken. By an anticonservative test, a drop in signal detection rate during the first block of vigilance behavior was significant. The performance during the last two blocks was not statistically different from control and the CO group means were close to those of the control group.

Winneke (1974) used a slightly modified version of the above task, using exposures of 0, 50 and 100 ppm CO, and failed to find any effects. The fact that the earlier study (a) used anticonservative statistics (b) showed an effect early but not late in exposure and (c) used very low levels of CO makes the nonreplication less surprising.

Beard and Grandstaff (1975) stimulated subjects with tone bursts and required to detect shorter-than-normal tones while exposed to either 0, 50, 175, or 250 ppm CO for a total of 50 minutes. The 50 and 175 ppm CO groups had significantly reduced performance (by an anticonservative test, but not after Bonferroni corrections were made). The 250 ppm group mean was nearly as good as the control group mean. Since results were not concentration related and anticonservative statistics were used,

these data are quite suspect. No attempt at replication has been reported.

Benignus et al. (1977) tested both short term memory and vigilance by requiring subjects to report numerals of differing parity in strings of three. Subjects were exposed to 0, 100 and 200 ppm CO for 3 hours and 20 minutes while the numerals were flashed on a display. COHb values for the three groups were 1, 4.6 and 12.6%. No statistically significant CO effects were found.

Sensory Effects. Sensory performance is quite sensitive to hypoxic hypoxia. CO exposure, too, has been reported to produce decrements in such behaviors. As is usual in CO literature, there is much disagreement among studies.

No effects of CO exposure upon the auditory sense have been reported. Perhaps this is because only two studies have been conducted, both of which used fairly insensitive dependent variables. Guest et al. (1970) reported that no changes in white noise flutter fusion were produced in subjects whose COHb reached 10%. Stewart et al. (1970) tested subjects exposed to 100 ppm CO for 8 hours (12% COHb) with standard screening audiograms and noted no effects.

The visual system has been extensively studied with respect to CO effects. The literature is, unfortunately, contradictory. The most obvious measure of visual function, the absolute threshold to light stimulation, has been reported to be unaffected by CO exposures up to 250 ppm for one hour (Beard and Grandstaff, 1975) but only four subjects were used and data were reported to be highly variable and statistics were not reported.

McFarland (1970), McFarland et al. (1944) and Halperin et al. (1959) reported an important experiment using trained subjects to reduce variability. They exposed subjects to short boluses of CO to rapidly raise COHb levels to 4.5, 9.4, 15.8 and 19.7%. At each increase in COHb, there was a small but reliable increase in visual threshold. Only four subjects were used and data were not well analyzed, nor were the studies conducted in a double-blind fashion.

Visual acuity, depth perception and color judgment have been reported to be unaffected by COHb levels of 12% (Stewart et al., 1970). Glare recovery in night vision or depth perception were not affected at 4.4% COHb (Wright et al., 1973). Ramsey (1972, 1973) reported that up to 12.1% COHb did not alter the visual difference threshold for brightness or depth perception. Critical flicker fusion has been studied widely and reported to be unaffected by CO exposure, in some cases high enough to produce 26% COHb (Fodor and Winneke, 1972; Guest et al., 1970; Lilenthal and Fugitt, 1946; O'Donnel et al., 1971b; Ramsey, 1973; Vollmer et al., 1946; von Post-Lingen, 1964). In a poorly documented study, four subjects were exposed to 0, 50, 150 or 250 ppm CO for one hour (Beard and Grandstaff, 1975). The authors reported concentration-related decrements in brightness-difference threshold, critical flicker fusion and visual acuity. Seppanen et al., (1977) used 1100 ppm transients of CO to raise the COHb of 22 subjects in steps to 13%. Beginning at 5% COHb, the critical-flicker-fusion threshold decrease in a concentration-related fashion.

A study by Beard and Wertheim (1967) demonstrated concentration related decrements in time discrimination for CO exposures of 0, 50, 100, 175 and 250 ppm. Several other experimenters, using similar but not identical protocols failed to show any decrements (O'Donnell et al., 1971b; Stewart et al., 1973). An almost exact replication by Otto et al. (1979) also failed to show any CO effects. The reason for the concentration-related finding of Beard and Wertheim is not clear. Their study was run in a single-blind fashion, however, and this could, conceivably, have produced the effects. Other studies using time estimation of different kinds, (O'Donnel et al., 1971b; Stewart, 1975; Stewart et al. 1975; Mikulka et al., 1970) found no effects of CO.

Motor Effects. Fine manual movements of various kinds were unaffected by COHb levels of less than 30% (Stewart et al., 1970, 1975) and lower levels (Wright et al., 1973; Fodor and Winneke, 1972; Winneke, 1974). Bender et al. (1971, 1972) reported, however, that when concurrent verbal behavior is required, Purdue Pegboard performance is affected at COHb levels of 7%. Ambulation was not affected at 6.6% COHb (O'Donnell et al., 1971a).

Tracking behavior is a well studied motor task and has been used to study CO. O'Donnel et al. (1971a) used a task requiring subjects to keep a meter needle centered as part of a multi-task battery but saw no reliable effects of COHb levels up to 12.7%. Putz et al. (1976, 1979) in two studies using two different protocols demonstrated a decrement in tracking with COHb levels of only 5%. Their task involved keeping a vertically moving spot

centered on a cathode ray tube (CRT). Benignus et al. (1986) have replicated the Putz et al. (1976) study using 8% COHb and have found similar results.

Several investigators have either simulated or used actual driving tasks during CO exposure. Most of these studies have shown no effects of CO even for 30% COHb (Forbes et al., 1937). More recent studies also reported no CO effects on actual automobile driving (Weir and Rockwell, 1973; McFarland, 1973). Wright et al. (1973) reported that transient exposure to 20,000 ppm CO (to produce 4.4 COHb) produced significant driving performance decrement. However, after Bonferroni corrections were made by the reviewer for anticonservative statistical analyses the effects were not significant. Rummo and Sarlanis (1974) used a driving simulator and exposures of 800 ppm prior to a 2 hour test period to produce 7.6% COHb at the beginning and 6.0% COHb at the end. This exposure to CO was reported to have increased reaction times to changes in lead-car speed.

Conclusions

The hypoxic effects of COHb elevation is, to some extent, compensated by simultaneous elevation in CBF. The fact that PtO_2 values fall as a function of COHb and the finding that some behaviors are decremented leads to the conclusion that the CBF compensation is not totally adequate.

Although wide range dose effects functions are not available for elevated COHb and many behaviors, it appears that fine motor functions are deleteriously affected at 5-8% COHb and perhaps at lower levels. It also is reported that visual dark adaptation is

impaired by COHb levels beginning at 5% COHb. Other behavioral functions have not been affected for similar levels of COHb or larger. Not much work has been performed with cognitive variables.

Since few dose effects functions are available, it is not possible to evaluate the cost of exceeding the threshold for effects with the exception of visual dark adaptation data. In the latter study only four subjects were used and they were highly trained. It seems unwise to base an estimated dose effects curve on one small study, especially since the study was performed in a single blind manner and has never been replicated. The latter consideration is especially important in a field of study in which so little consistency among studies is found.

CARBON MONOXIDE (HYPERBARIC)

No studies were found on motor, sensory or cognitive effects of CO exposure in hyperbaric conditions. Since the effect of COHb, however, is taken to be one of hypoxia, it would appear that the effects would be predictable via COHb prediction at elevated pressure, in addition to the effects of hyperbaric air itself. Since no empirical tests of this generalization are available, further speculation is considered too hazardous.

DISCUSSION AND CONCLUSIONS FOR CO_2 AND CO

Due to lack of quantitative or reliable estimates of the effects of CO on CNS function, it would be unwise to speculate about the effects in combination with CO_2 and/or hyperbaric air. The conclusions drawn for CO_2 and hyperbaric air are much safer.

The major question for the issue of CO in combination with other atmospheric components is whether the effects of CO would be additive or interactive. Since the effects are on the O_2 delivery system, it may be that effects would be on the same CNS systems as are affected by hyperbaric air or CO_2 although there is not evidence on the point. If, however, COHb elevation did affect the same CNS systems, the effects would be at least additive.

SOLVENT VAPORS

The list of solvents, hydrocarbons and refrigerants which might possibly occur in any modern mechanized environment is incredibly long and probably constantly changing. To review the effects of such a list of chemicals on CNS function is a task beyond the scope of rationality. What is required is a unifying principle under which the substances in question can be considered and which will make possible an overview and appropriate generalizations.

The neurotoxic effects of many solvents are akin to the effects of anesthetics and, in fact, many of them have found specific use in that function. This class of anesthetics appears to act on the CNS with much the same effect as inert gases. This contention is not intended to imply that the mechanism of action is the same as inert gas. If the effect on CNS function of solvents is like that of anesthetics and of inert gasses, however, then much generality can be observed.

The following review will discuss effects of solvents in the context of their inert gas- and anesthetic-like effects. The contention of similarity among solvents and anesthetics will be briefly defended. A model solvent (toluene) will be reviewed

indepth. Corollary observations will be made regarding other solvents.

Toluene

Pharmacokinetics

Toluene can enter the body via inhalation of its vapors, by ingestion, by injection and by skin absorption, to a minor extent. It is exhaled, unchanged, as toluene and excreted in urine as hippuric acid. Toluene is distributed widely throughout the body and since it is lipophilic, organs containing lipids act as reservoirs (Sato et al., 1974). The rate of rise of toluene level in various organs was proportional to their vascularization and the diffusion rate of toluene into tissue (Astrand, et al, 1975) as well as metabolic rate and instantaneous concentration gradients (Cohr and Stokholm, 1979). In richly vascularized areas such as brain, heart, liver, and kidney, concentrations were reported to rise at almost the same rate as in blood. In poorly vascularized areas such as bone marrow and adipose tissue, asymptotic levels were reached more slowly (Cohr and Stockholm, 1979).

Benignus et al. (1984) studied toluene levels in blood and brain of rats after exposure to toluene vapors. A single compartment pharmacokinetic model was fitted to the data. Toluene reached its asymptotic level in blood and brain at the same time, about 60 minutes after the start of exposure. Elimination to 10% of maximum value required 240 minutes. Whole brain tissue levels were higher than blood levels, probably because of lipid retention. Functions were provided for the

estimation of brain and blood toluene levels as a function of exposure levels form 50 ppm to 1000 ppm toluene in air.

Toluene is metabolized in several ways but mainly is converted to benzoic acid by oxidation of the methyl group of toluene via benzyl alcohol and benzaldehyde in the microsomes of liver parenchymal cells (Cohr and Stockholm, 1979). Benzoic acid is conjugated with glycine to form hippuric acid (80%) and with glucuronic acid to form benzoylglucuronide (20%) which are readily water soluble and eliminated via the kidney. About 80-85% of total toluene is eliminated via urine. Small quantities of toluene are apparently converted to phenolic compounds (Cohr and Stockholm, 1979). Depending upon the relative concentration in inspired air and blood, toluene also passes across the alveolar membrane to be excreted via expired air.

CNS Functional Effects

Benignus (1981 a,b) reviewed the CNS effects of toluene. The following are excerpts from those reviews and from the later literature. Only the effects of short term exposure will be considered in the present literature summary.

General Observations and Activity. Toluene exposures in humans have not been systematically studied at high levels. Subjects (Von Oettingen et al, 1942 a,b) reported fatigue, headache, paresthesia, slowed pupillary reflex and confusion for toluene levels between 200 and 600 ppm and all of the above plus "hilarity", "exhilaration" and nausea for toluene levels of 600-800. Reports of industrial accidents and of toluene abuse (similar to glue sniffing) provided data on high-level exposure in man. Such effects as dizziness were reported at 200 ppm

exposures and mild incoordination at exposures of 500-1,500 ppm toluene in an industrial setting. (Wilson, 1943). During early stages of habituation to toluene, abusers were reported to exhibit dizziness and sometimes fear but during later stages of habituation, the symptoms progressed toward euphoria and indifference. (Sugimoto, 1973). Rats exposed to 1,000-4,000 ppm toluene for 4 hours during sleep showed decreased slow-wave sleep time and increased paradoxical sleep at 1,000 ppm and other sleep disturbances at higher levels (Takeuchi and Hisanaga, 1977). Similar disturbances were reported which became progressively more extreme over a 24 week period for rats exposed to 2,000 ppm toluene for 4 hr/day (Takeuchi et al., 1977). Toluene exposures of 4,000 ppm, 2 hr/day for 60 days produced no notable effects on wheel running or on open-field activity in rats (Ikeda and Miyake, 1978). Locomotor activity in mice was not affected at 100 ppm but 1000 and 3000 ppm produced time related increases in activity (Bushnell et al., 1985).

Operant or Learning Studies. Toluene effects on aversively controlled behavior have been reported. Rats were previously trained on shock-avoidance exposed to 0, 1,000 or 3,000 ppm toluene for 4 hours, then removed from the exposure chamber and tested for 1 hour (Shigeta et al, 1978, 1980). Marginal decreases in interresponse times in the 3,000 ppm group occurred. Bar-press shock-avoidance performance was reported to have shown "decrements" beginning at 3,200 ppm toluene (Krivanek and Mullin, 1978).

Various appetitive schedules of reinforcement have also been used to evaluate toluene effects. Rats were repeatedly exposed over the course of the study to 150 ppm toluene for 1/2, 1, 2 and 4 hours, during which the rats performed previously learned bar press responses (Geller et al., 1979). In the 1 hour exposure session, response rates increased in all subjects. During the 4 hour session, subjects showed a decrease in rate. These results could be interpreted as providing evidence for an inverted U-shaped time-and/or concentration-effects function. Two recent studies using mice exposed to toluene have reported inverted U-shaped concentration-effect curve. Time dependent schedules of reinforcement were used (Moser and Balster, 1981; Glowa, 1981). Exposure concentrations of near 1000 ppm to toluene produced maximum response rates. Mean response rates in a speed dependent bar press task were reduced in a concentration related manner in rats exposed to toluene beginning at 570 ppm (Colotla et al., 1979).

Human Performance. Humans were exposed for 20 minutes to 100, 300, 500 and 700 ppm toluene and tested in reaction time tasks (Gamberale and Hultengren, 1972). Increased reaction time was observed to be dose related beginning at 300 ppm. Toluene exposure of 80 ppm had no effect upon tracking and visual search tasks (Cherry et al., 1983). Similarly, up to 100 ppm toluene did not produce decrements in a wise variety of sensory motor or cognitive tests (Anderson et al., 1983). Decreased control of voluntary eye movements and increased saccadic movements were reported in human subjects exposed to about 120 ppm were reported by Hyden et al. (1983). Baelum et al. (1985) reported that 100

ppm toluene exposure produced fatigue and feelings of intoxication, accompanied by decreased manual dexterity, color perception and visual discrimination accuracy. Toluene exposure of about 70 ppm was reported to have not affected reaction time, and short term memory (Olson et al., 1985).

Conclusions. Many of the subjective symptoms of toluene exposure are similar to those of inert gas narcosis. As with inert gas exposure, toluene exposure produces decrements in timing behavior on rate dependent schedules in laboratory animals. In man, toluene produces increased reaction time and decreased motor dexterity. There are not enough data to estimate the relative effect of toluene on motor as compared to cognitive function. The threshold for toluene effects in man appears to be 100-200 ppm.

Comparison of Solvents.

A number of articles have been published comparing the effects of various solvents. Only a recent representative few of these articles will be reviewed. Paksy et al. (1982) compared the effects of toluene, benzene and m-xylene in the rat. All of the solvents produced ataxia with varying degrees of potency. Similarly, all of them produced a concentration related effect on ambulation, running wheel and open field activity although the effects of toluene and, to a lesser extent m-xylene, were often of the inverted U-shape curves. The different curve shapes may have been due to the relative potency and the particular concentrations studied.

The effects of toluene and hexane were compared by Pryor et

al. (1983) in rats. Conditioned avoidance behavior was impaired by both with varying degrees of potency. Hexane, however produced grip strength decrements which toluene did not. This difference could be reconciled if the potency for peripheral neuropathy were greater for hexane. Toluene and n-hexane produce very similar changes in CNS levels of acetylcholine (increase), choline acetyltransferase (reduction) and acetylcholine esterase (increase). N-hexane was more potent than toluene but the course of changes were the same (Honma, 1983).

Kjellstrand et al. (1985) studied activity levels in mice exposed to either toluene, methylene chloride, perchlorothylene, trichloroethylene or 1,1,1-trichloroethane. All of the solvents produced similar increases at various concentrations, thus indicating only a potency difference. Moser and Balster (1985) tested mice in an inverted screen test using toluene, 1,1,1-trichloroethane and ethanol. Again, all produced effects and only differences in potency were observed.

It would appear that the behavioral and CNS effects of various acute exposures to solvents are similar in kind. The differences seem to be in the potency of various solvents. It should be emphasized that much comparative work is required before (a) it can be assured that solvents are similar for all CNS effects (b) all solvents behave as above and (c) relative potency estimates become available. Conclusions about the similarities are premature, but, not contradicted.

Speculations About Interactions With Inert Gas Narcosis, CO_2 and CO Toxicity

No studies on the effects of simultaneous exposure of solvents with CO_2, CO or inert gas narcosis have been found. The question of interactions is further compounded by lack of information about either the effects of or the pharmacokinetics of solvents at hyperbaric pressures. Since the behaviors (and presumably) the CNS functions which are affected by inert gas narcosis are also affected by solvents, it is not unreasonable to expect that the effects would be additive. Too little data are available to warrant quantitative projections. Indeed, speculation about additivity of effects are without empirical ground.

FIGURE LEGENDS

Figure 1. Decrement in motor and cognitive performance (in percent of control) as functions of percent CO_2.

Figure 2. Projected effects of CO_2 and hyperbaric air on motor performance (in percent of control). Caution. The plots are based upon projections and do not represent actual data.

Figure 3. Projected effects of CO_2 and hyperbaric air on cognitive performance (in percent of control). Cuation. The plots are based upon projections and do not represent actual data.

Figure 4. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 5 liters per minute, at 1 atm.

Figure 5. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 10 liters per minute, at 1 atm.

Figure 6. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 20 liters per minute, at 1 atm.

Figure 7. Projected COHb formation as a function of time for 25 ppm CO in normobaric air, at alveolar ventilation rates of 5-20 lpm.

Figure 8. Projected COHb formation as a function of time for 25 ppm CO in air, compressed to 5 atm, at alveolar ventilation rates of 5-20 lpm.

Figure 9. Projected COHb elimination in normobaric air for alveolar ventilation rates of 5-20 lpm.

Figure 10. Projected COHb elimination at 5 atm pressure for alveolar ventilation rates of 5-20 lpm.

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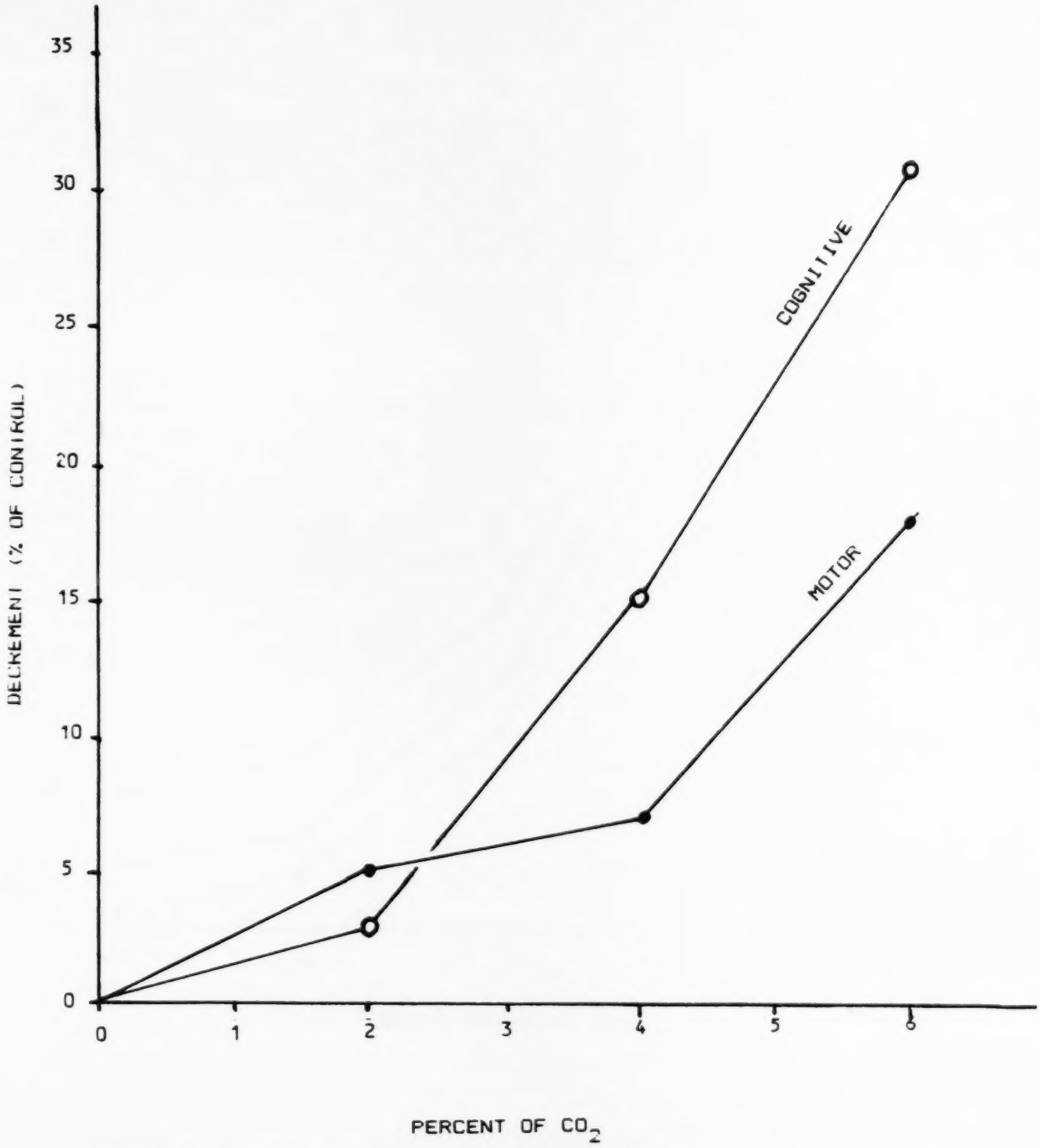

Figure 1. Decrement in motor and cognitive performance (in percent of control) as functions of percent CO_2.

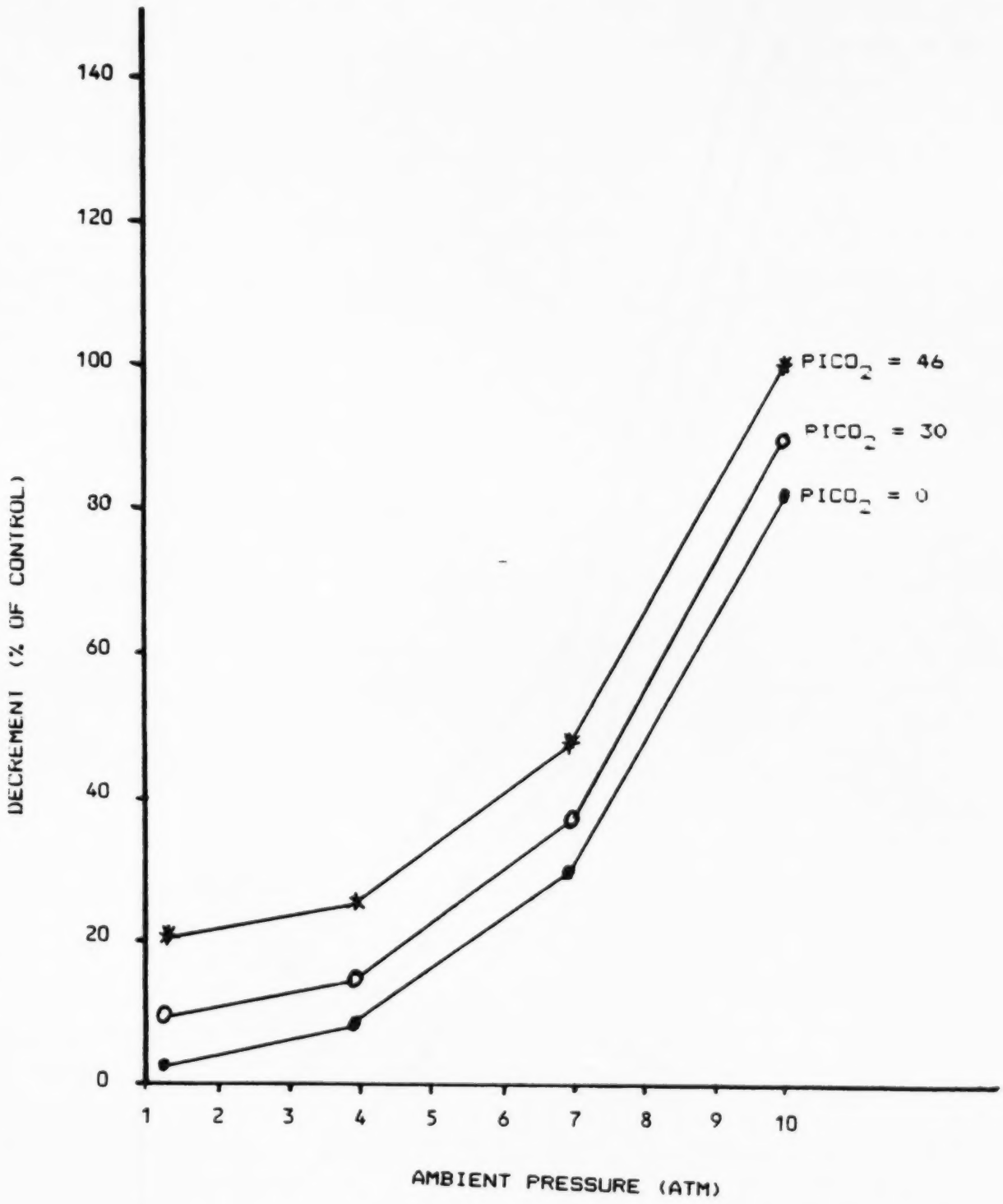

Figure 2. Projected effects of CO_2 and hyperbaric air on motor performance (in percent of control). Caution. The plots are based upon projections and do not represent actual data.

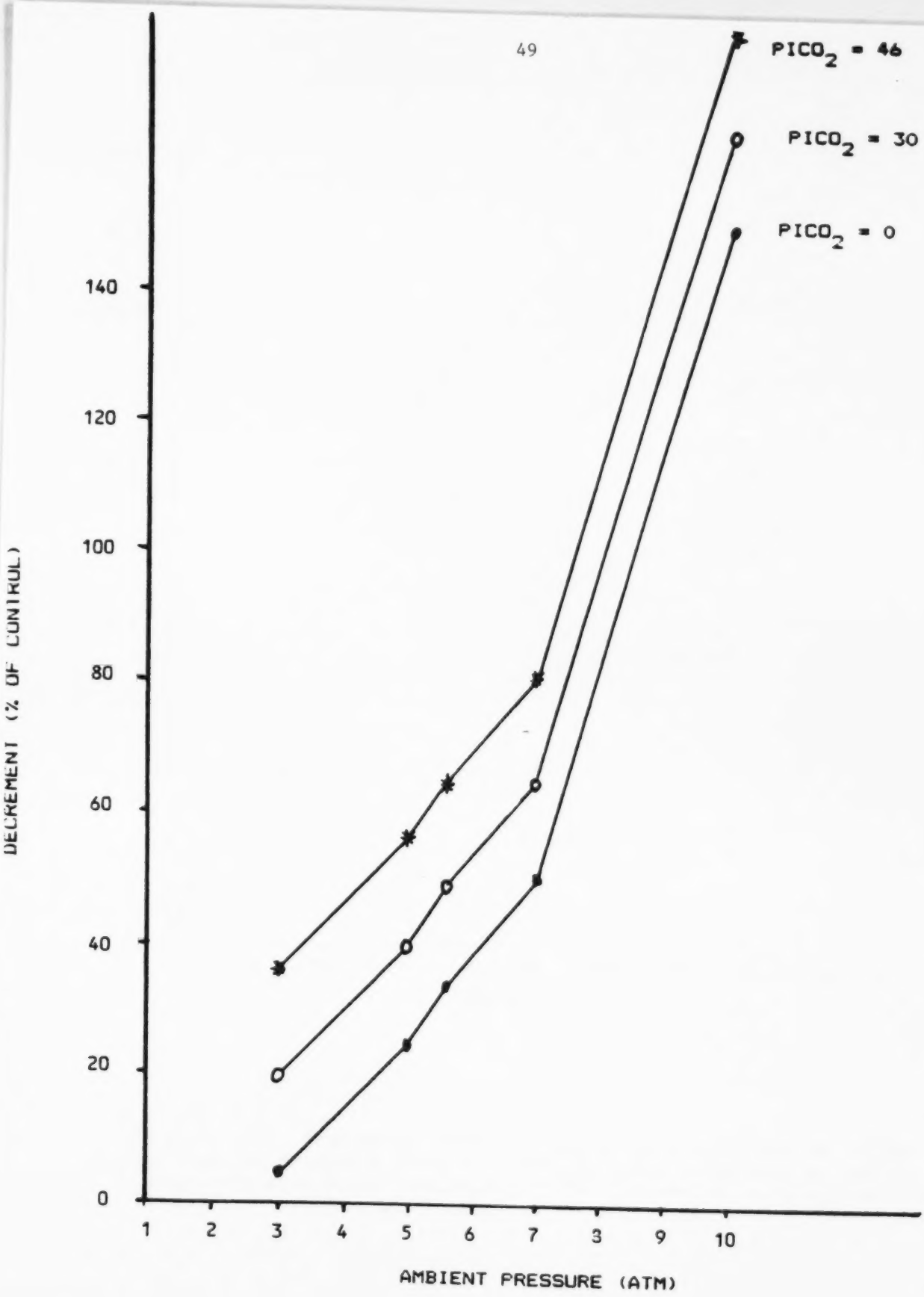

Figure 3. Projected effects of CO_2 and hyperbaric air on cognitive performance (in percent of control). Cuation. The plots are based upon projections and do not represent actual data.

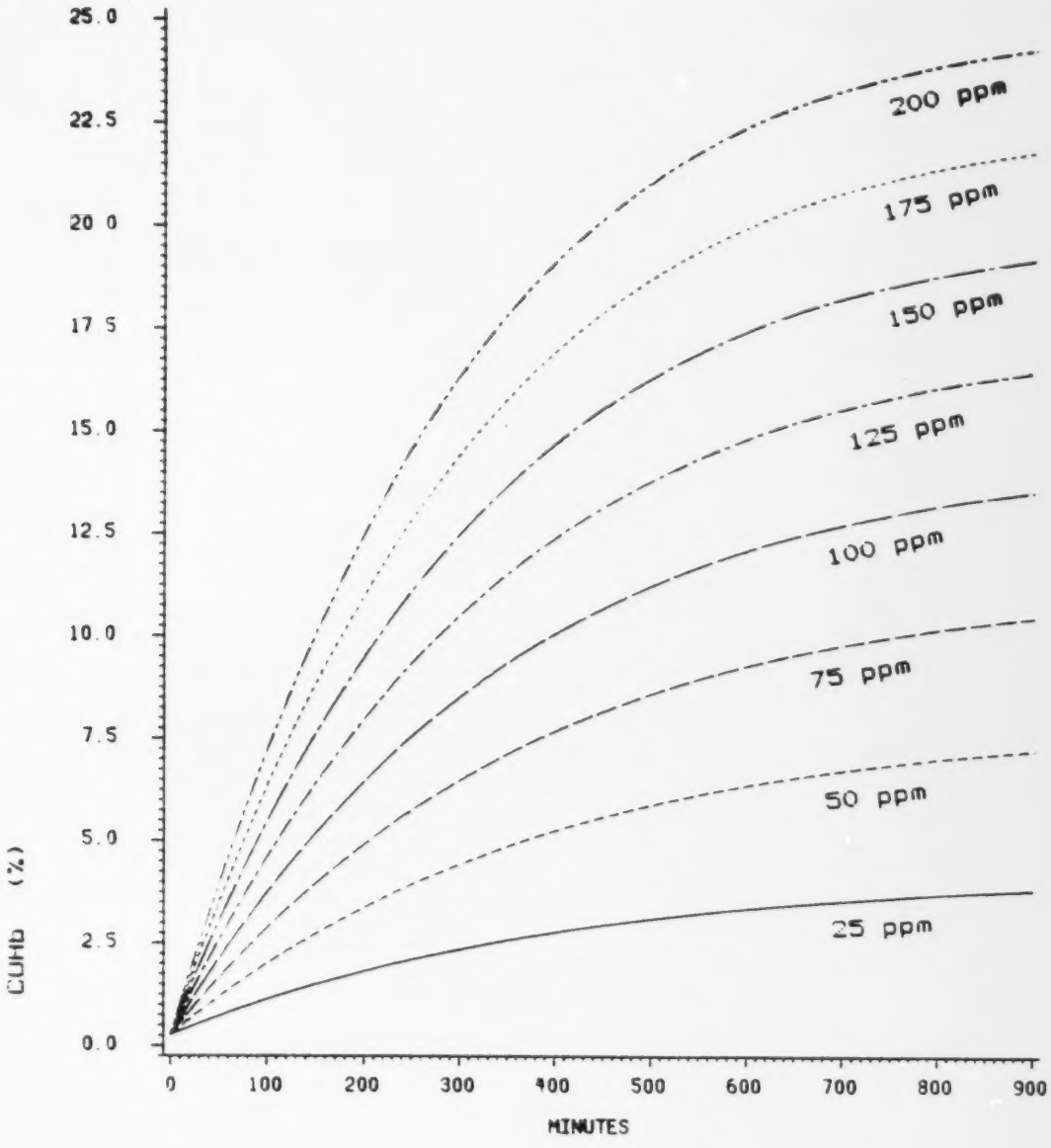

Figure 4. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 5 liters per minute, at 1 atm.

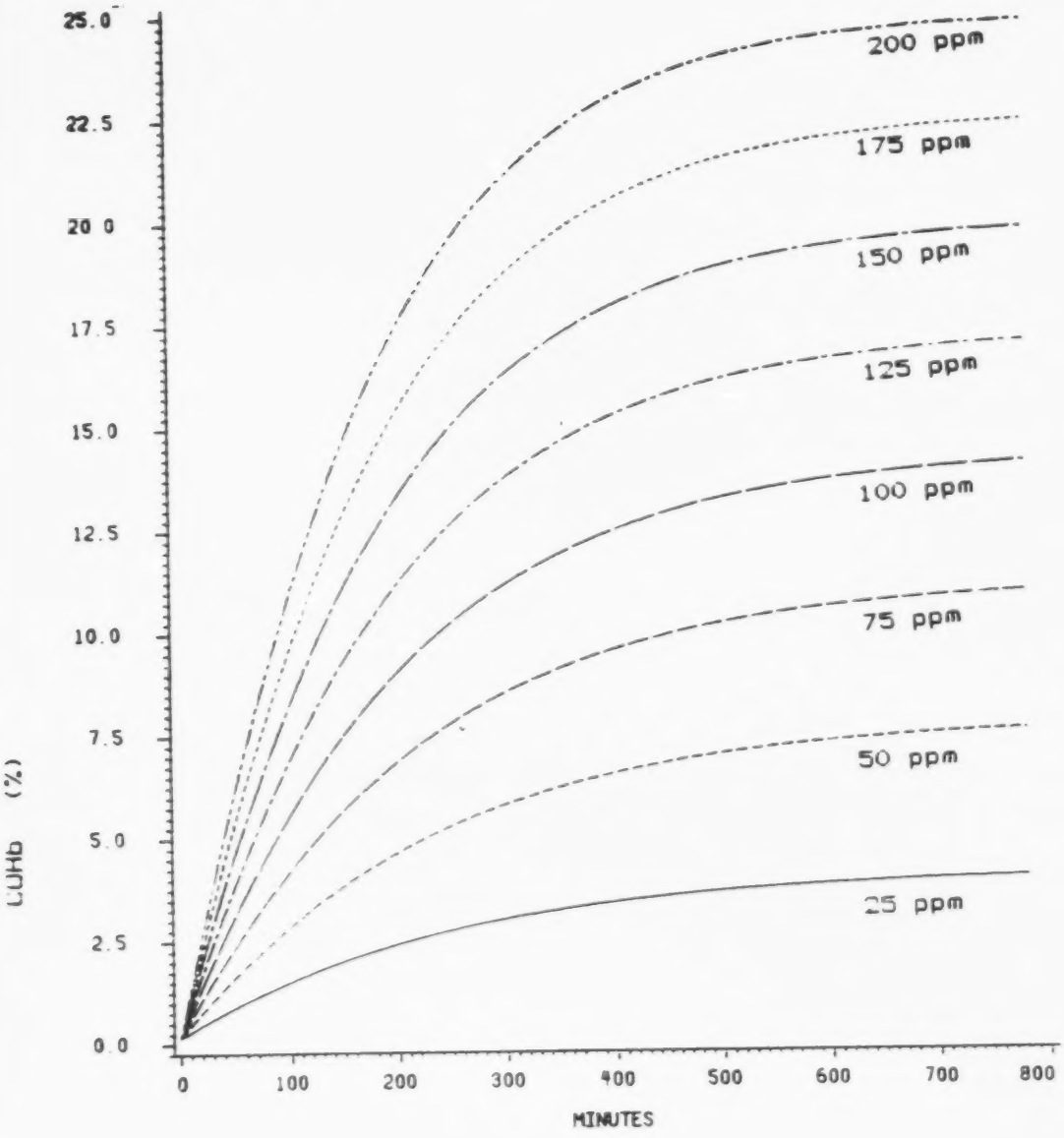

Figure 5. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 10 liters per minute, at 1 atm.

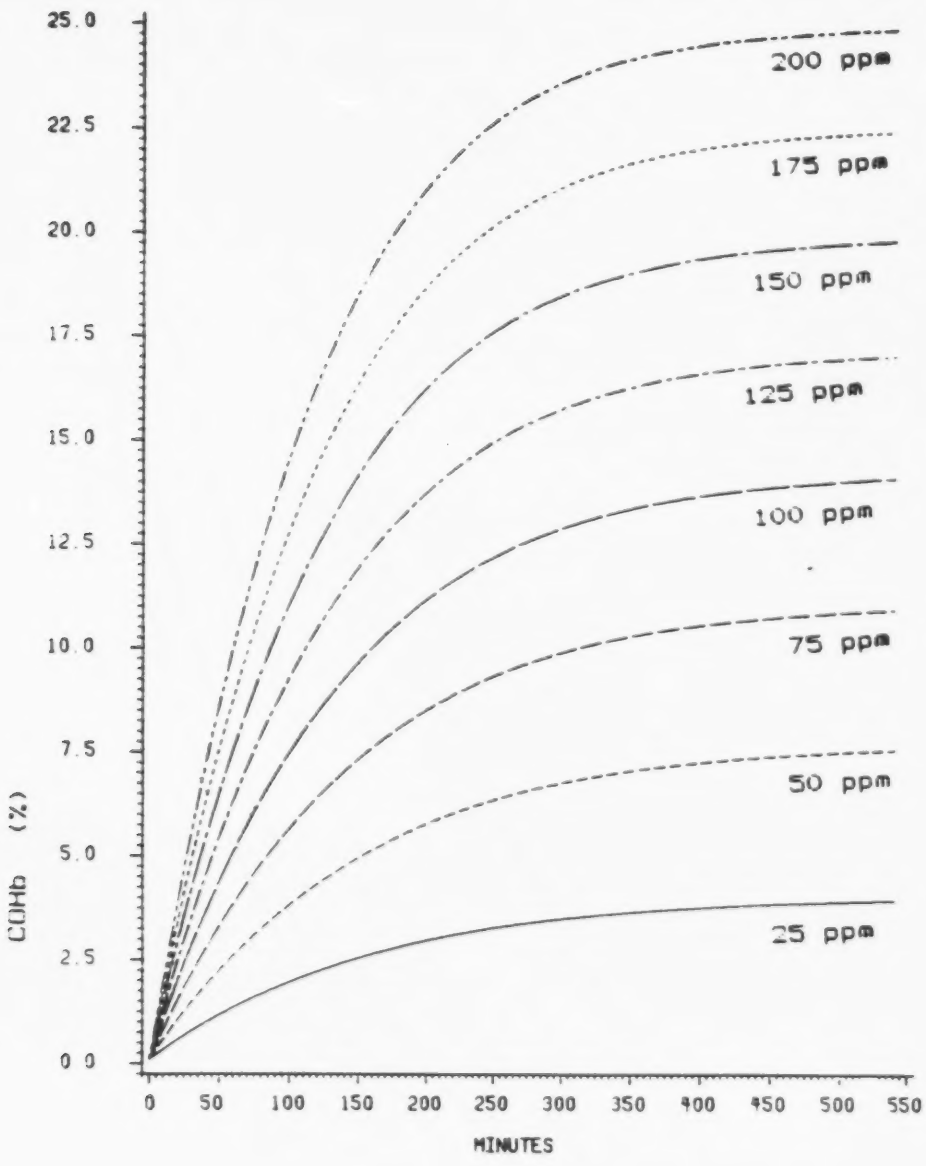

Figure 6. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 20 liters per minute, at 1 atm.

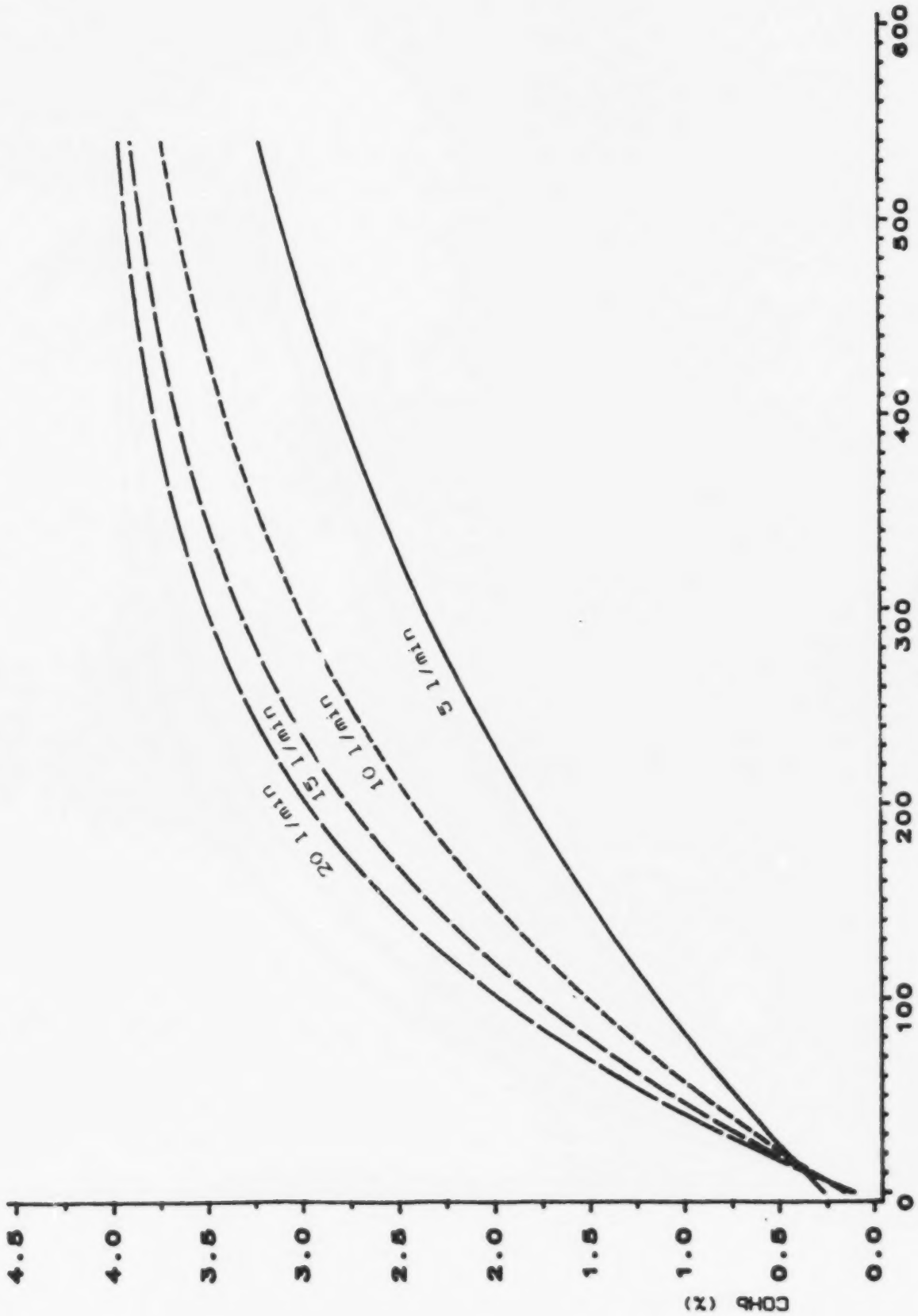

Figure 7. Projected COHb formation as a function of time for 25 ppm CO in normobaric air, at alveolar ventilation rates of 5-20 lpm.

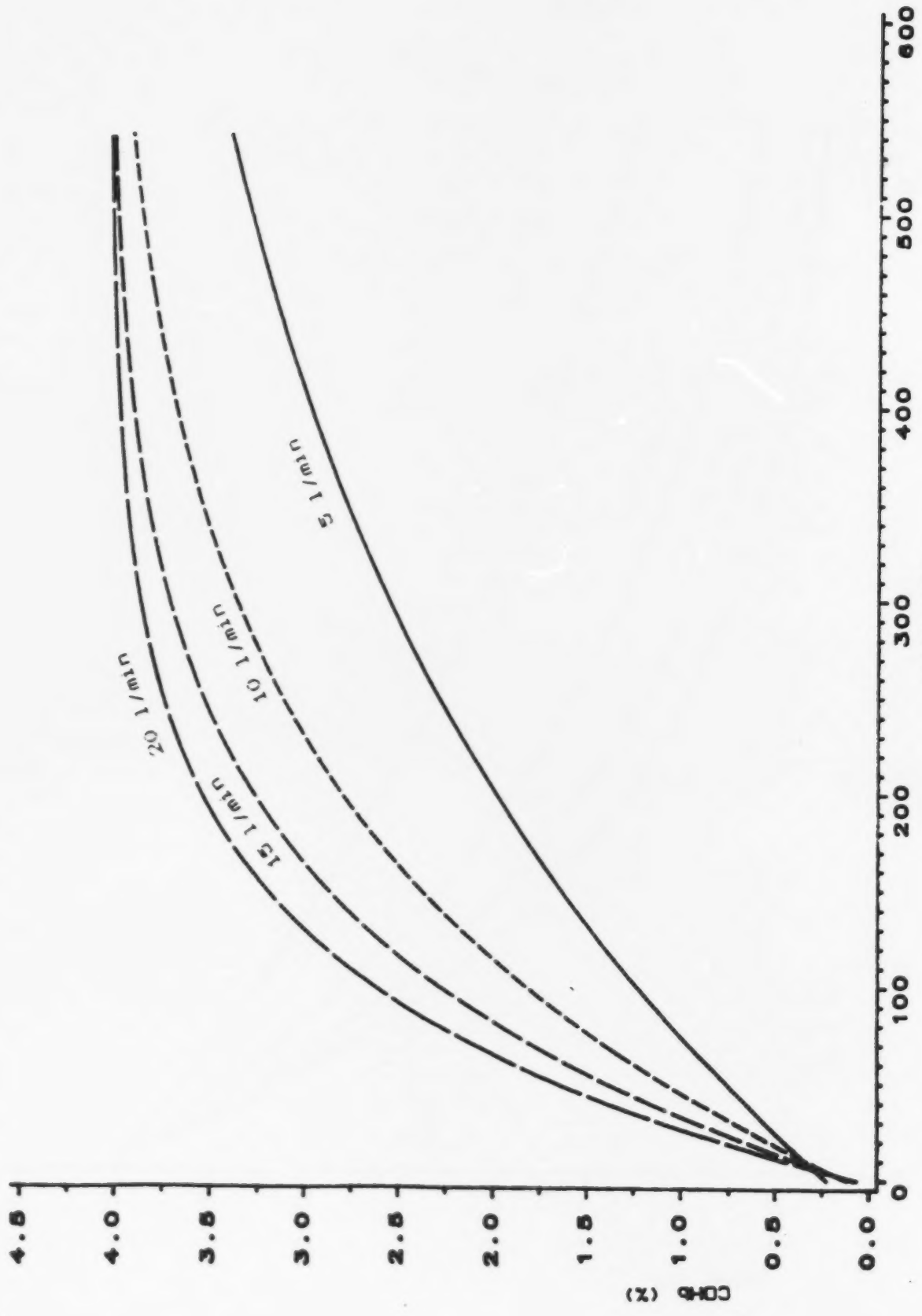

Figure 8. Projected COHb formation as a function of time for 25 ppm CO in air, compressed to 5 atm, at alveolar ventilation rates of 5-20 lpm.

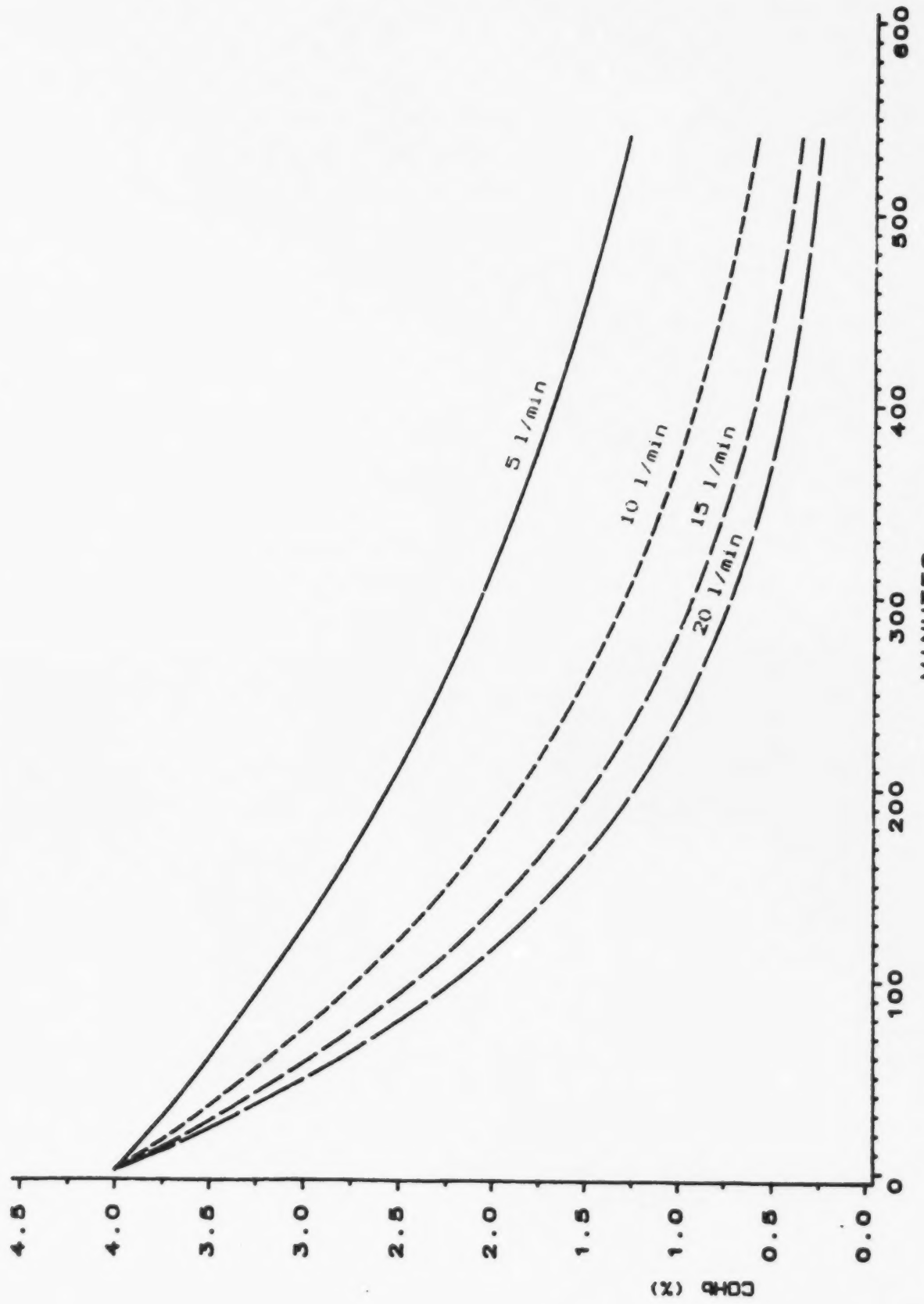

Figure 9. Projected COHb elimination in normobaric air for alveolar ventilation rates of 5-20 lpm.

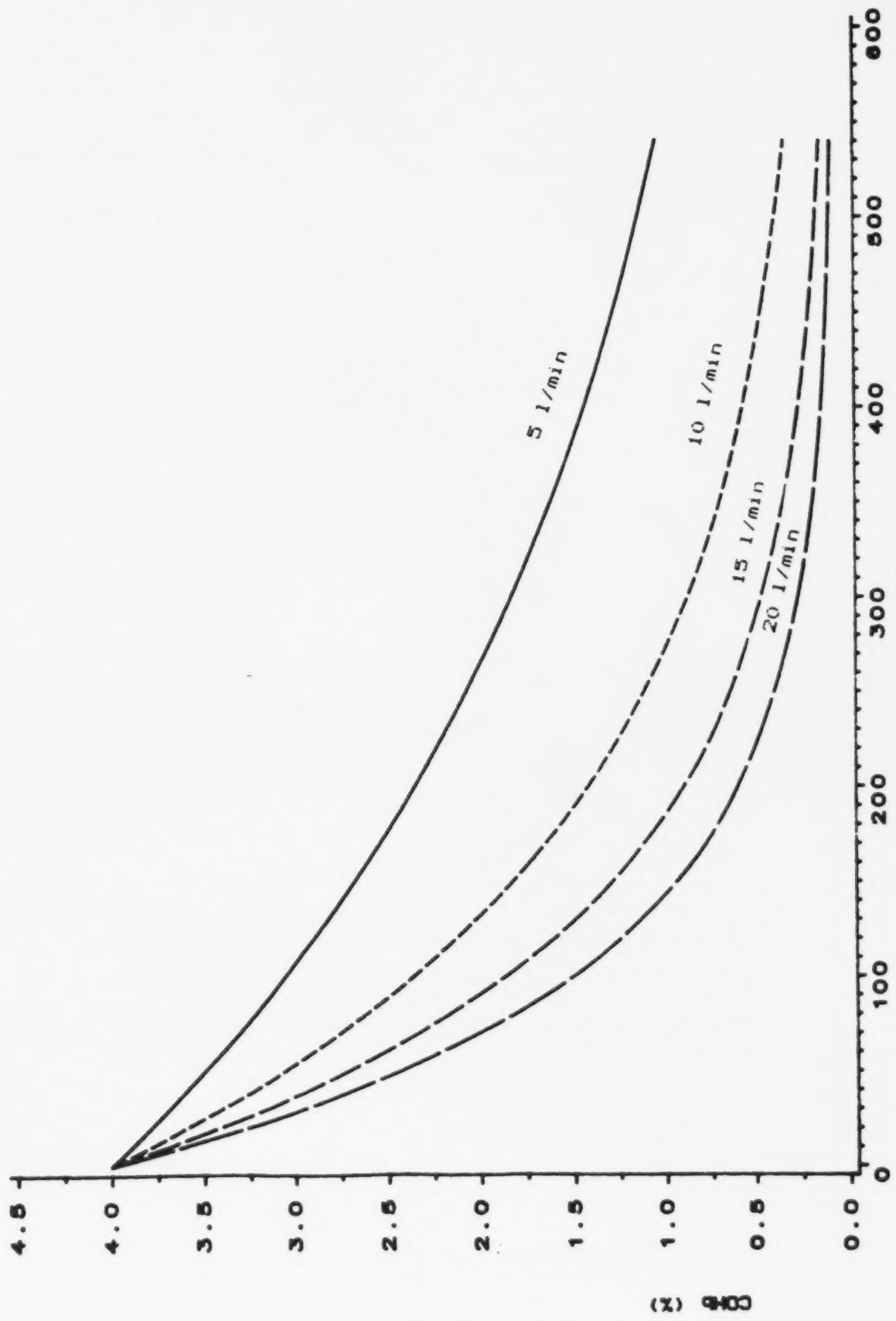

Figure 10. Projected COHb elimination at 5 atm pressure for alveolar ventilation rates of 5-20 lpm.

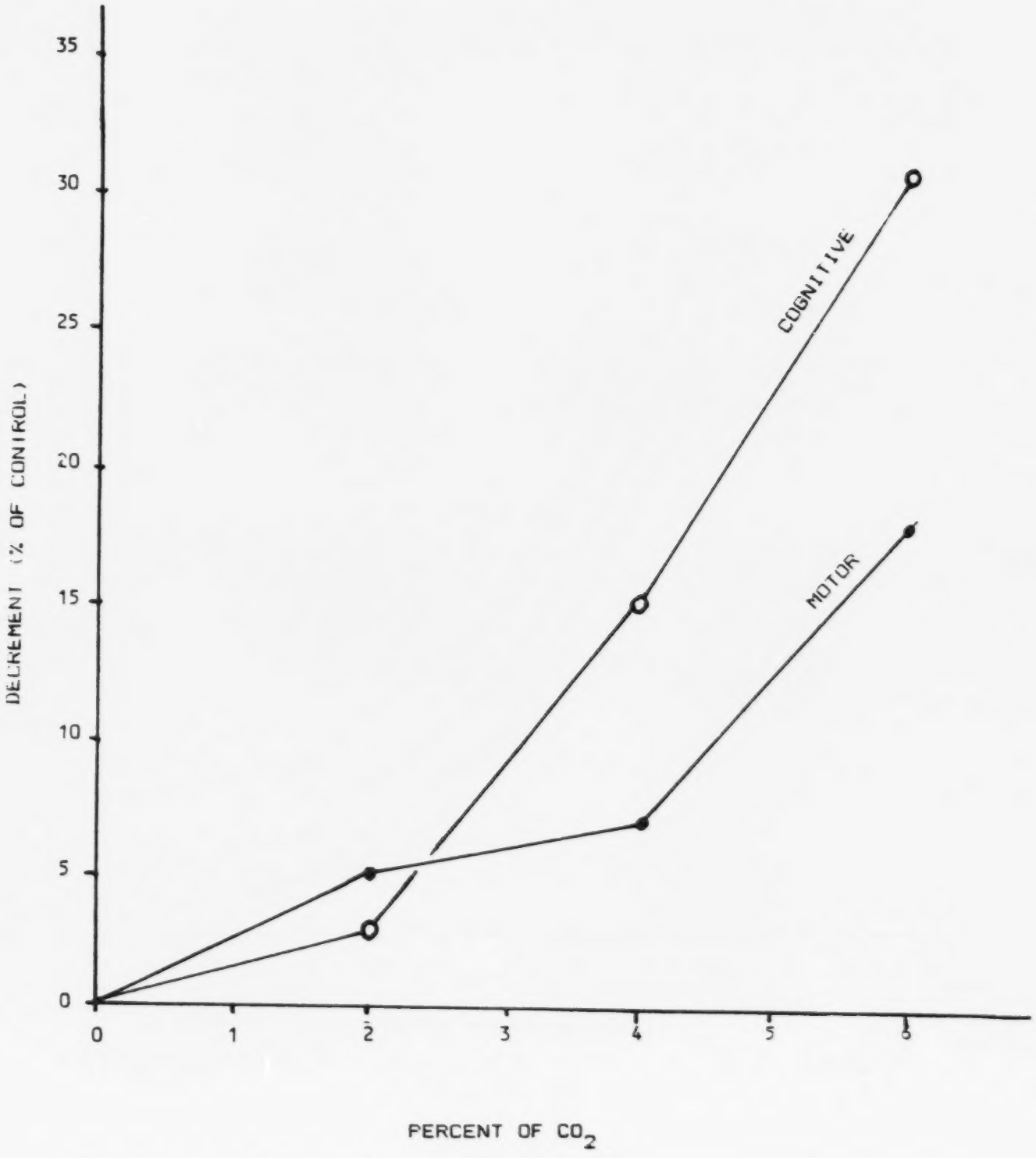

Figure 1. Decrement in motor and cognitive performance (in percent of control) as functions of percent CO_2.

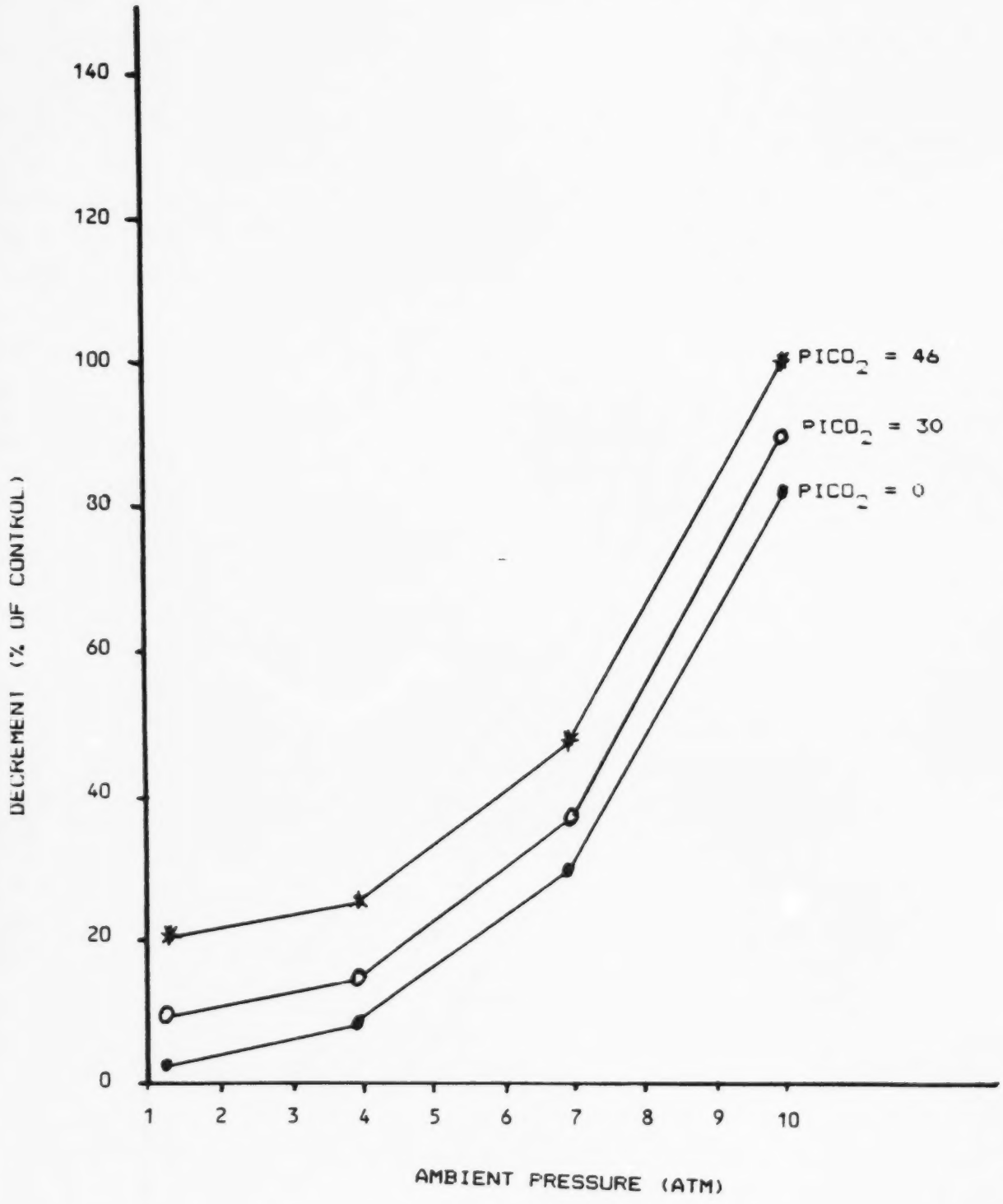

Figure 2. Projected effects of CO_2 and hyperbaric air on motor performance (in percent of control). Caution. The plots are based upon projections and do not represent actual data.

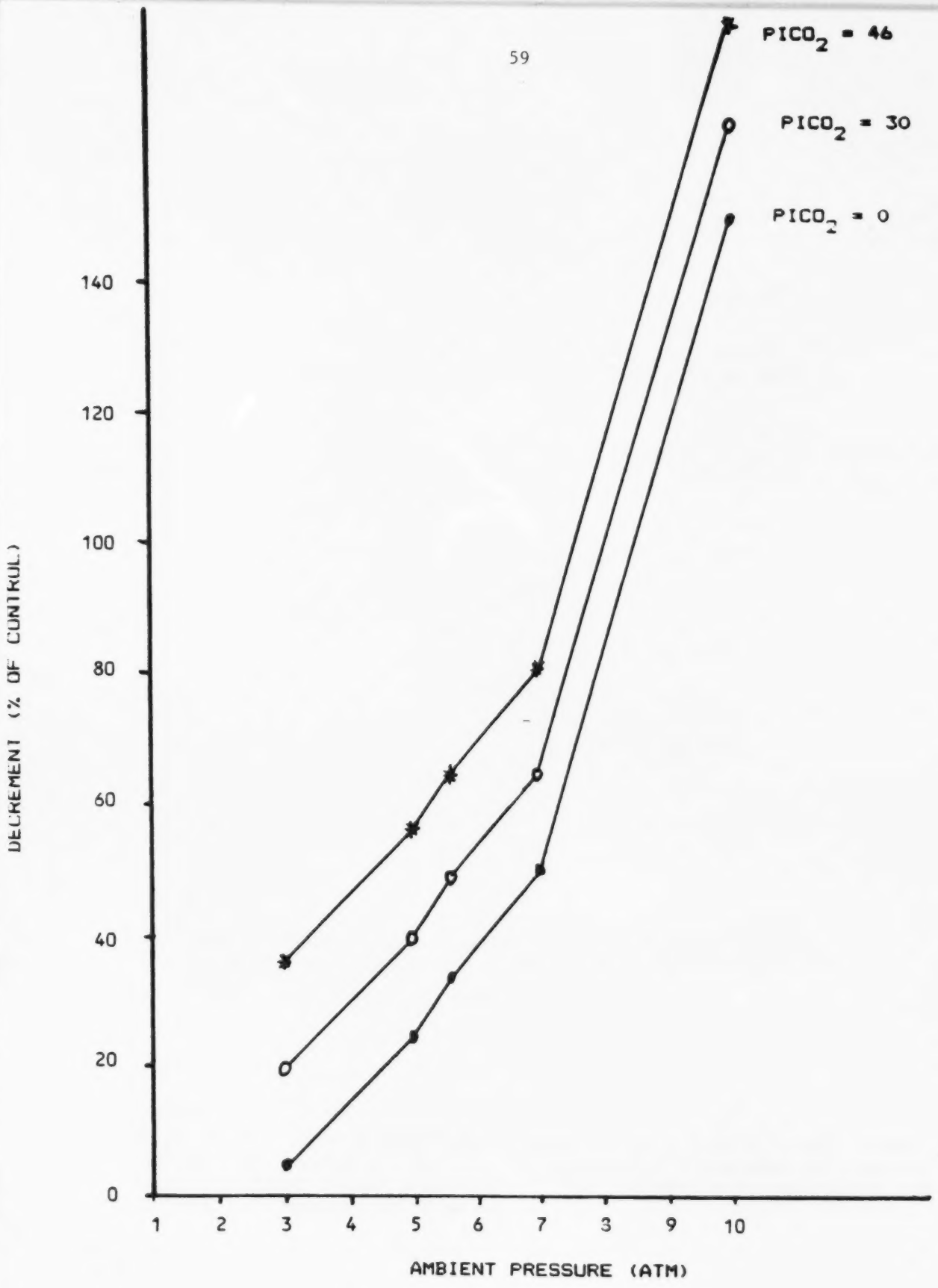

Figure 3. Projected effects of CO_2 and hyperbaric air on cognitive performance (in percent of control). Cuation. The plots are based upon projections and do not represent actual data.

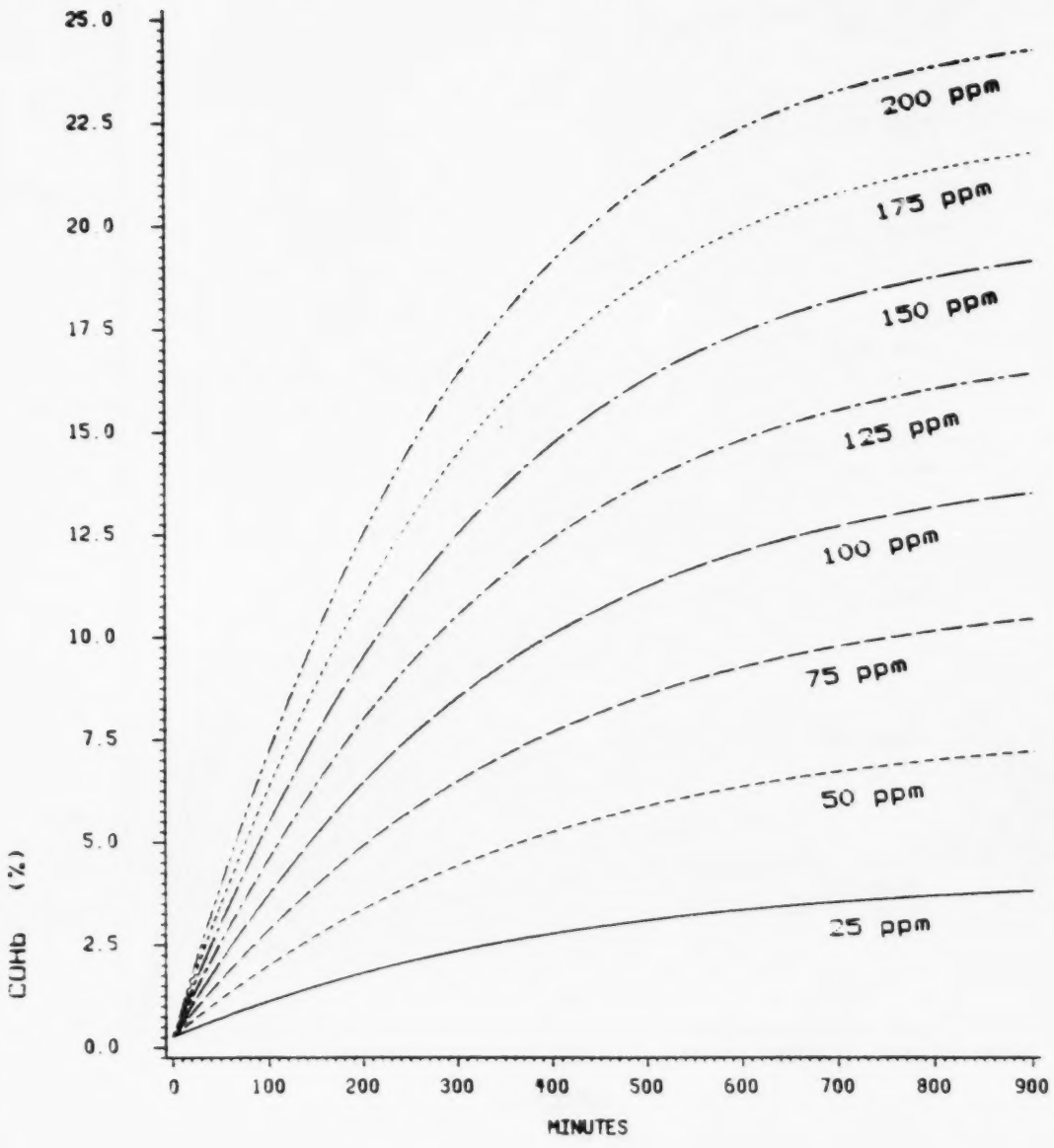

Figure 4. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 5 liters per minute, at 1 atm.

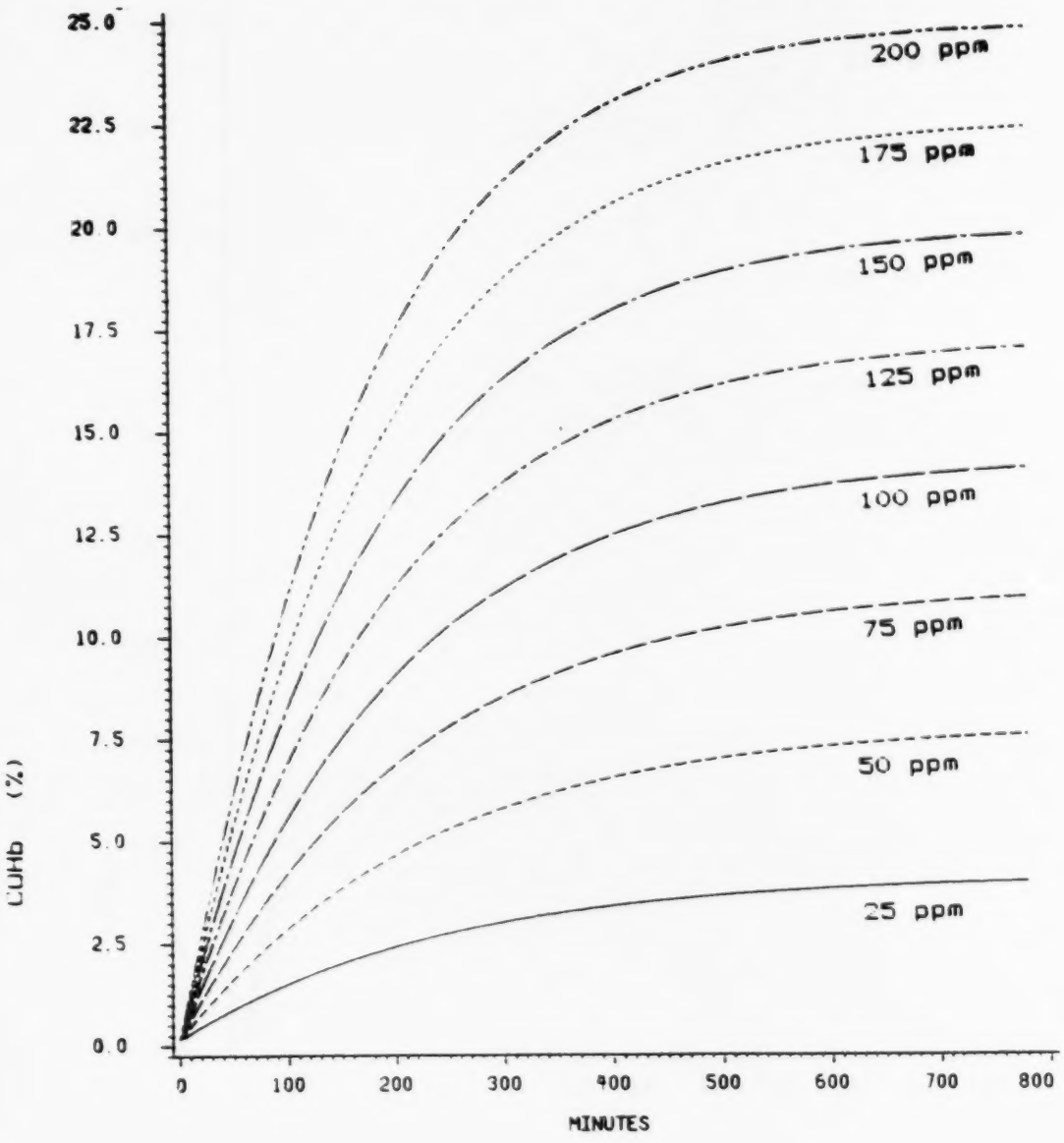

Figure 5. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 10 liters per minute, at 1 atm.

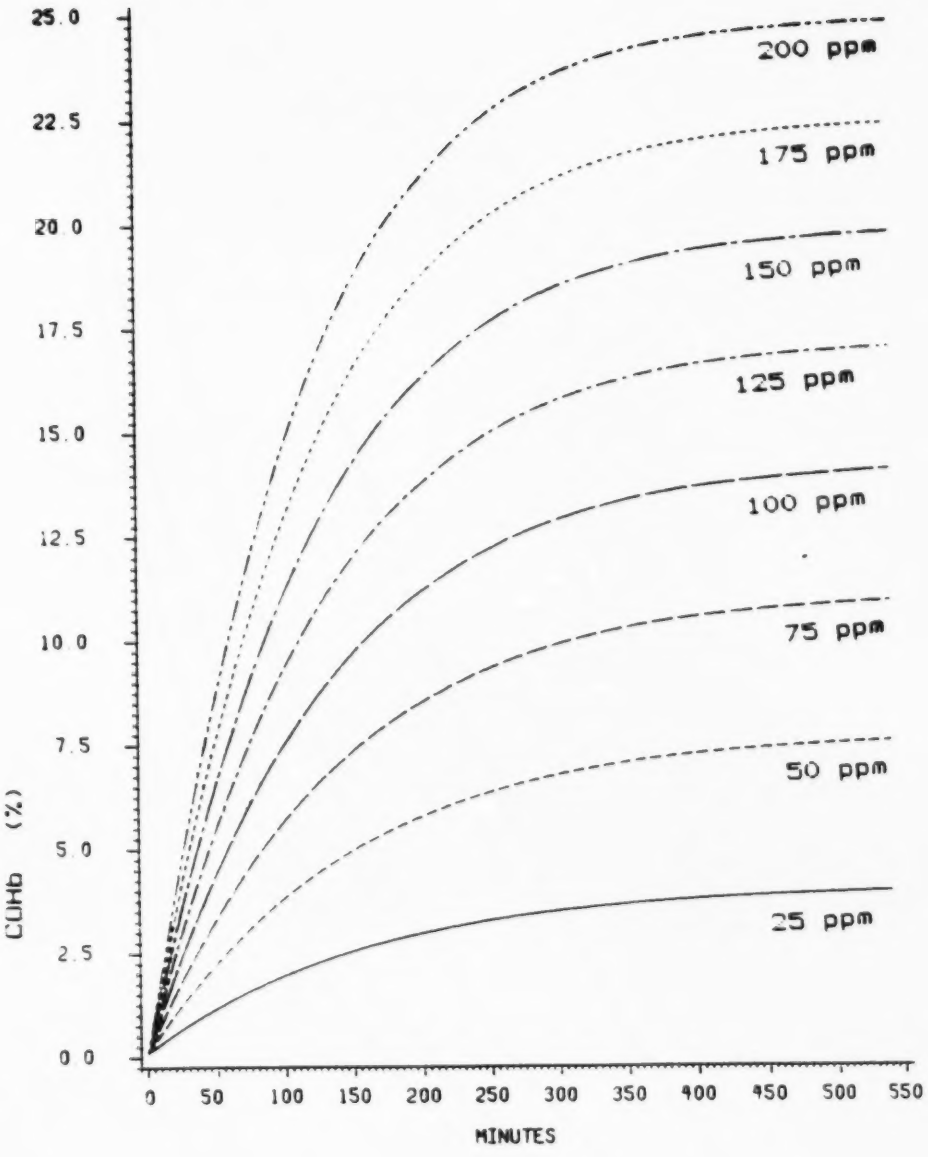

Figure 6. Projected COHb formation as a function of time for various CO exposure levels. Projections generated by use of the Coburn-Forster-Kane equation. For alveolar ventilation of 20 liters per minute, at 1 atm.

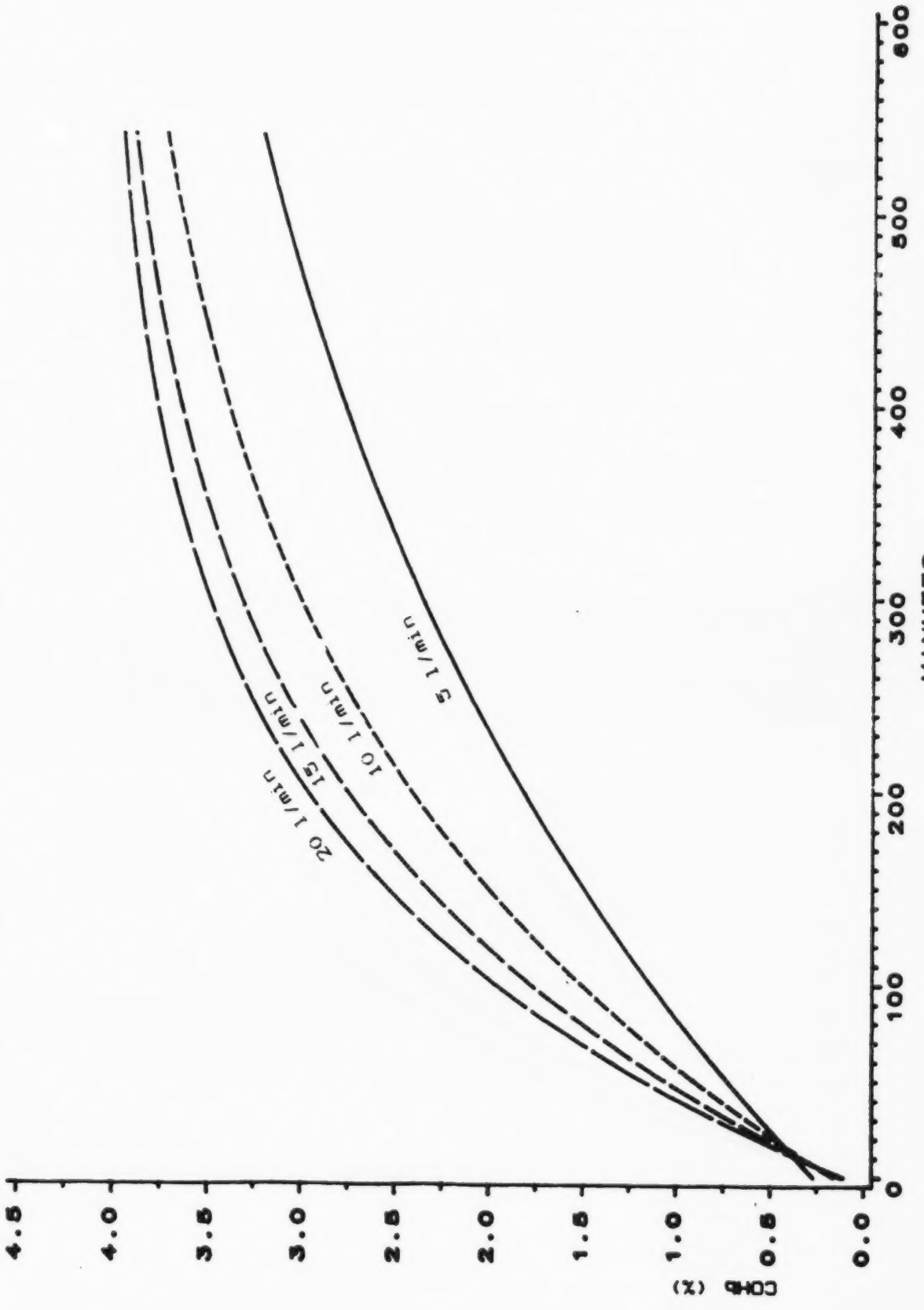

Figure 7. Projected COHb formation as a function of time for 25 ppm CO in normobaric air, at alveolar ventilation rates of 5-20 lpm.

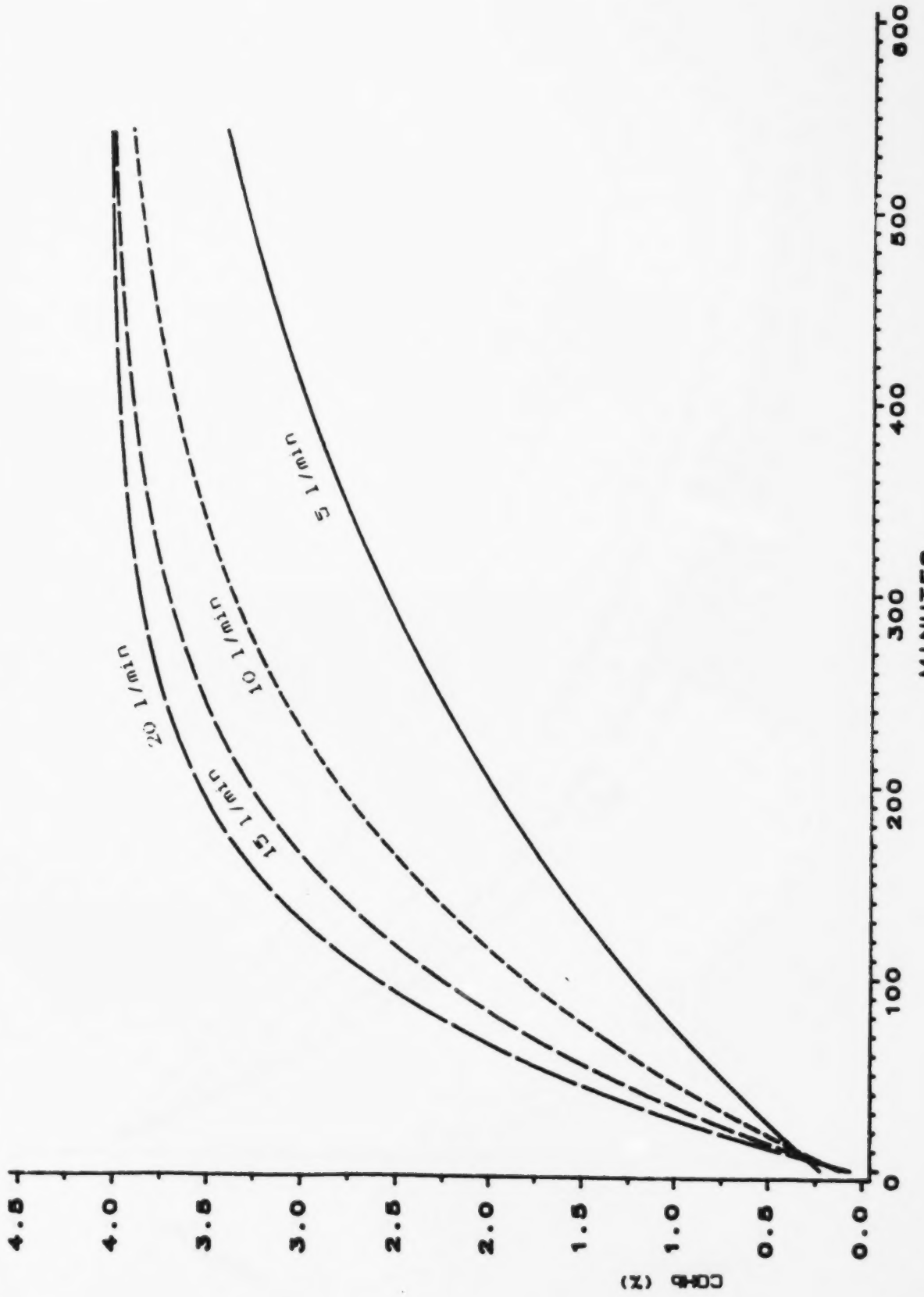

Figure 8. Projected COHb formation as a function of time for 25 ppm CO in air, compressed to 5 atm, at alveolar ventilation rates of 5-20 lpm.

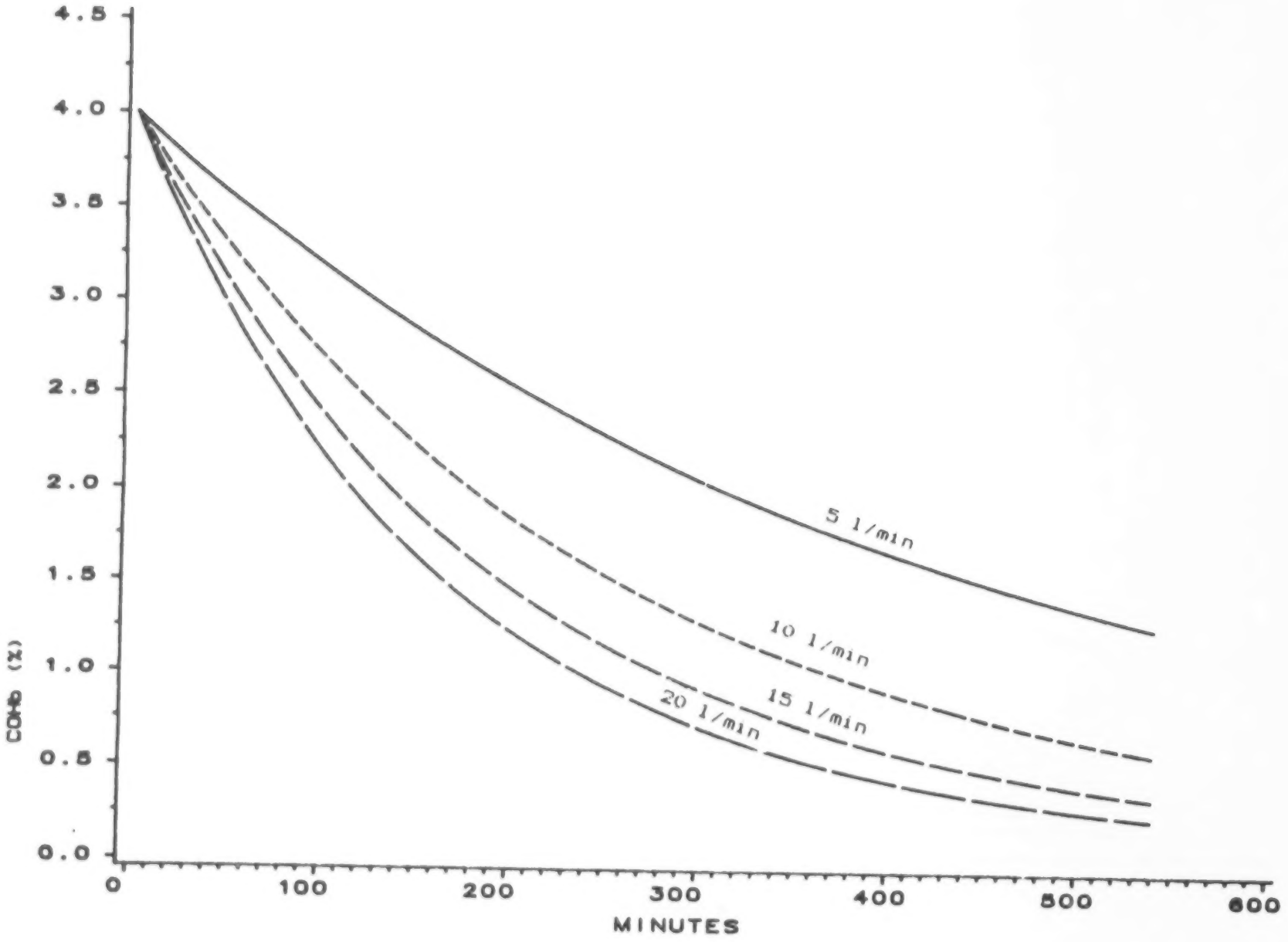

Figure 9. Projected COHb elimination in normobaric air for alveolar ventilation rates of 5-20 lpm.

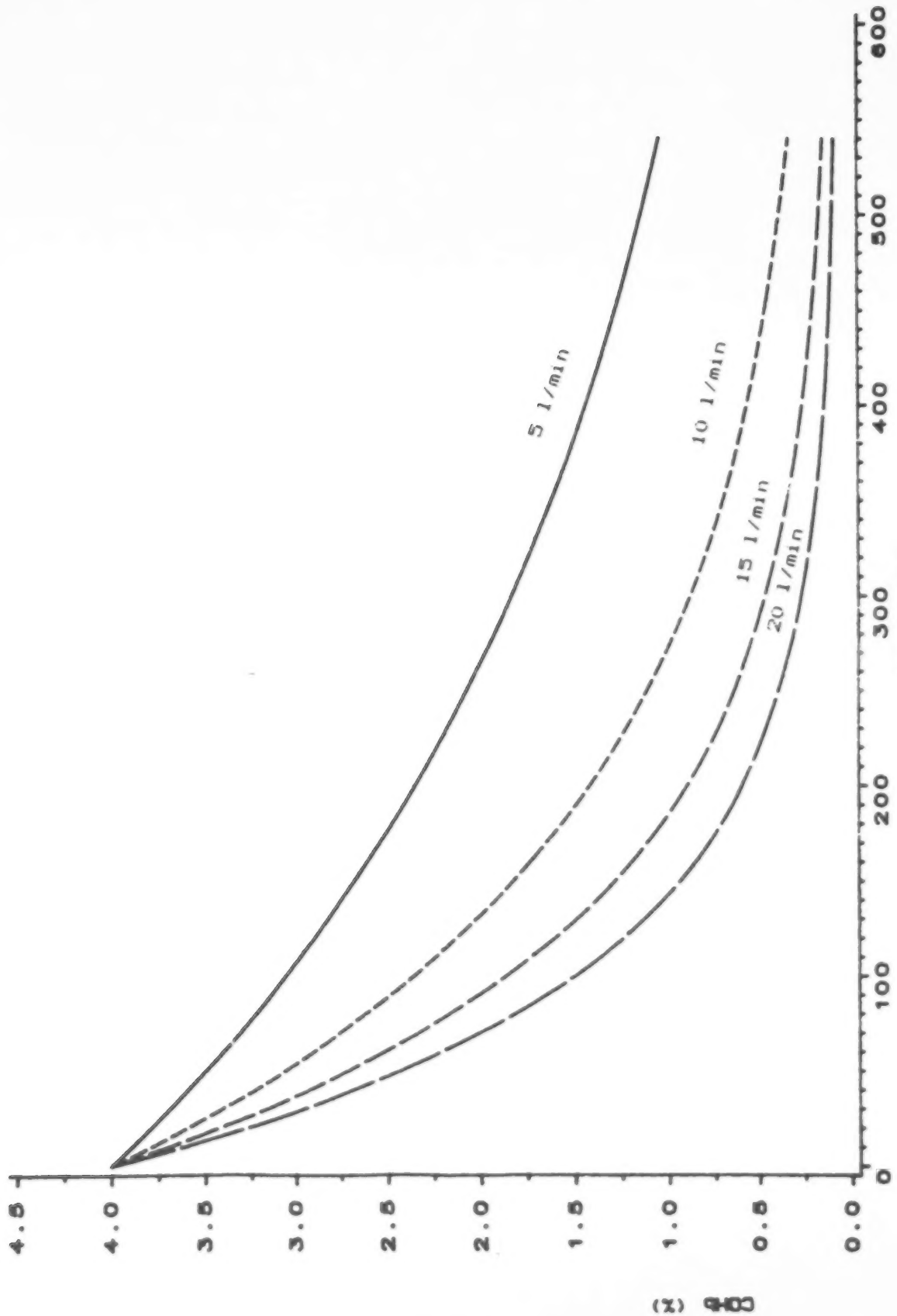

Figure 10. Projected COHb elimination at 5 atm pressure for alveolar ventilation rates of 5-20 lpm.